Molecular Modeling

Target Protein

Reference Molecules

Disease

Receptor-Based Design

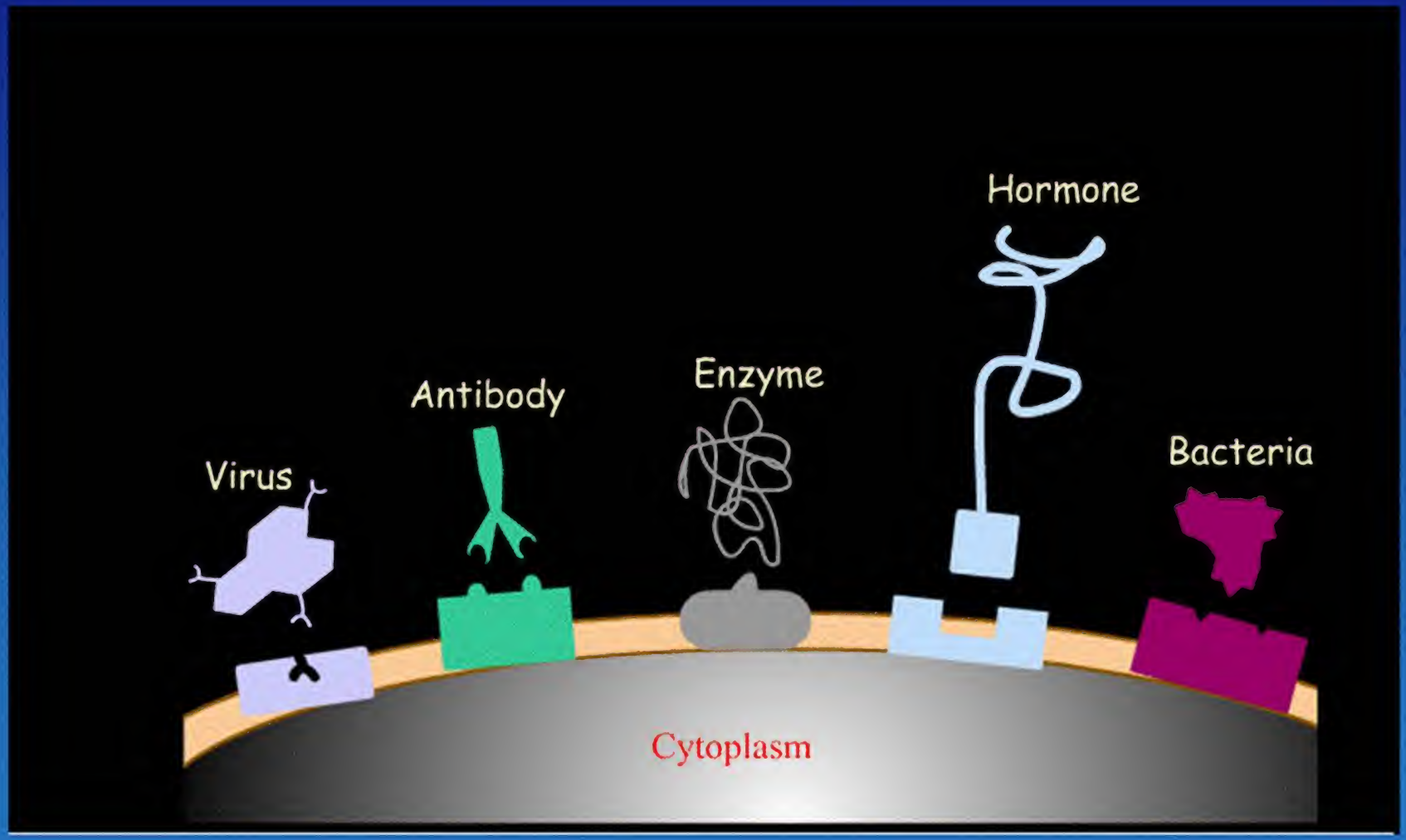
Molecular Complementarity

Pharmacophore-Based Design

Molecular Mimicry

Molecular Modeling

Diseases

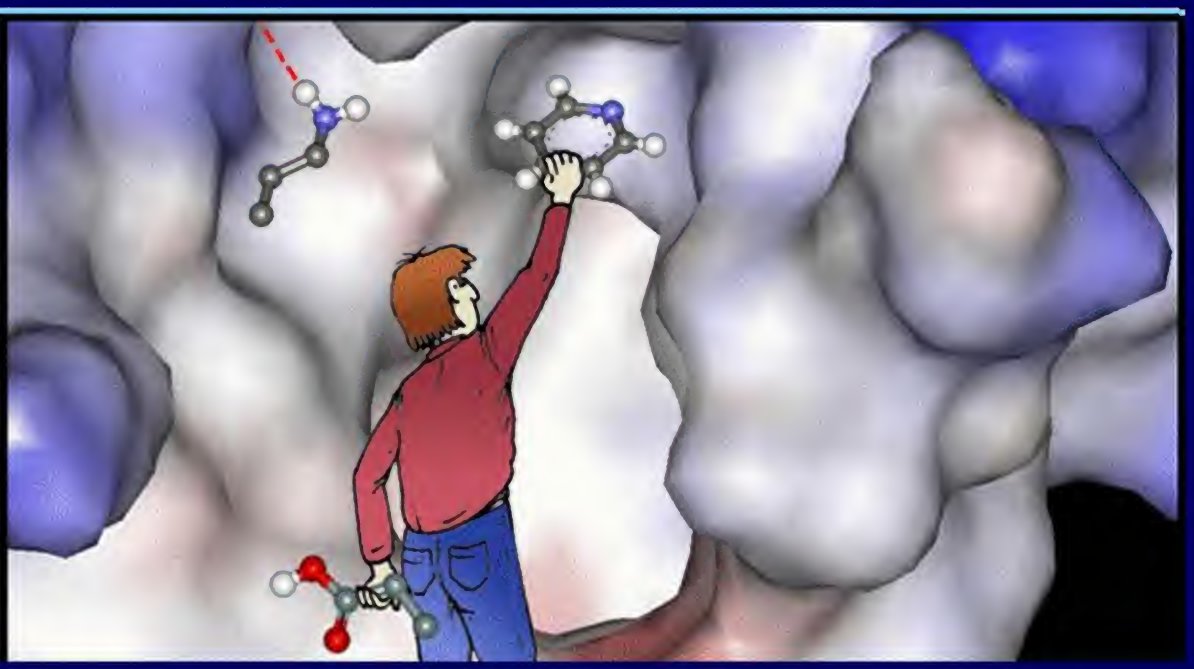


Molecular Modeling

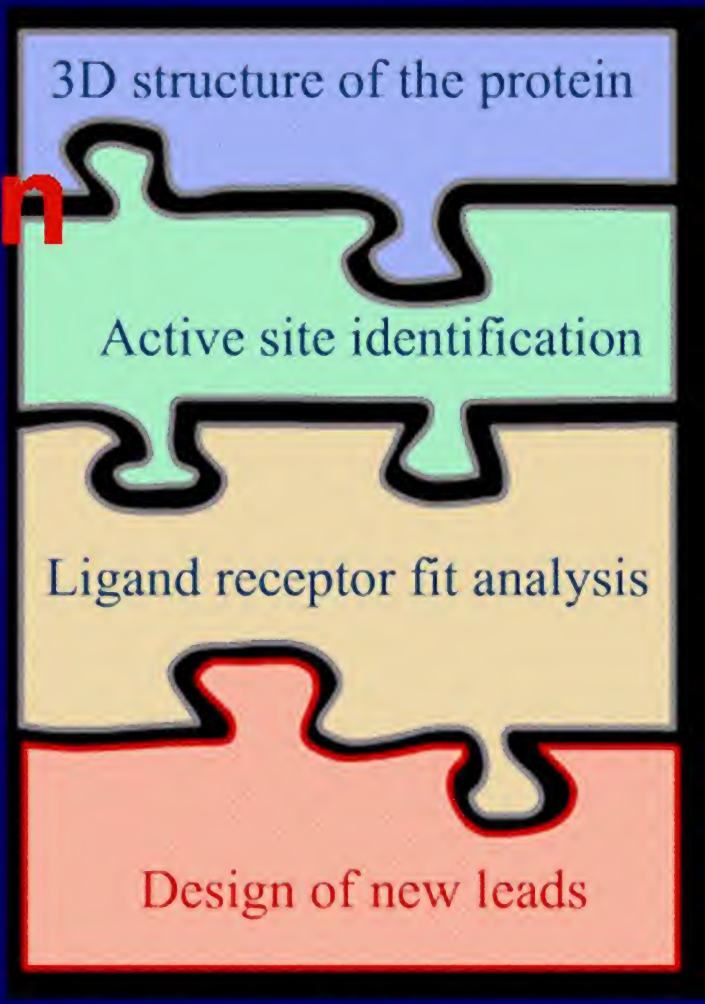
Reference
Molecules

Disease

Target Protein

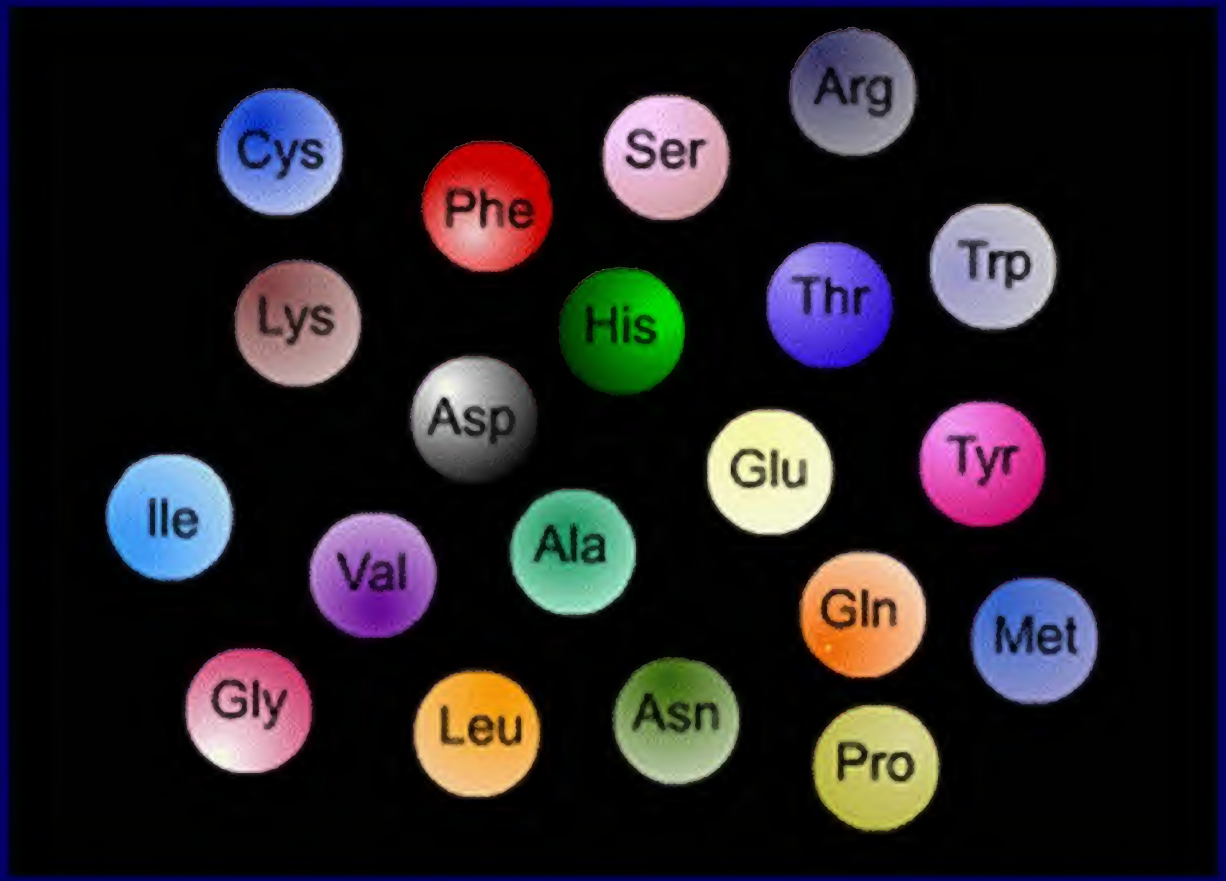


Protein

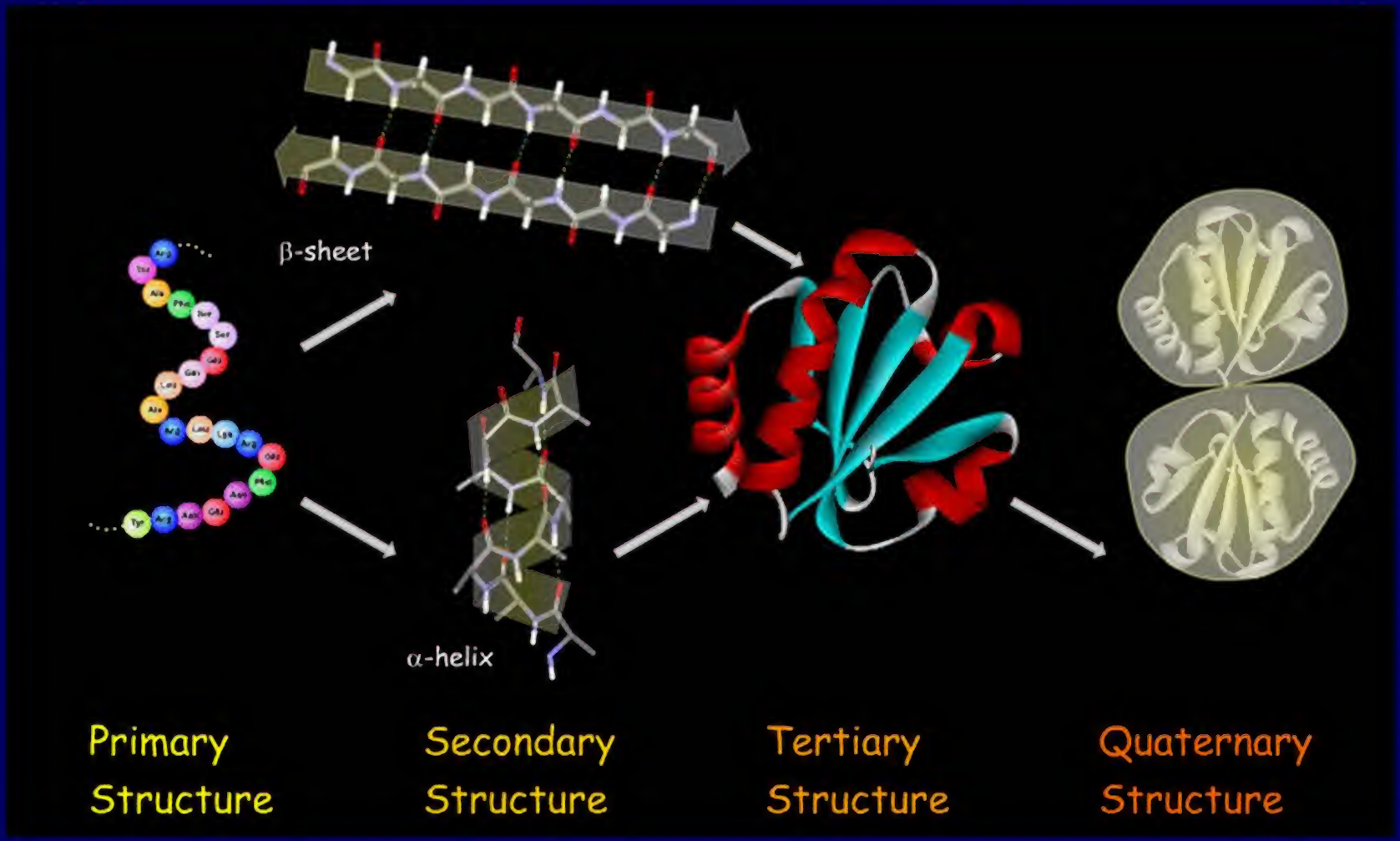


Target Protein

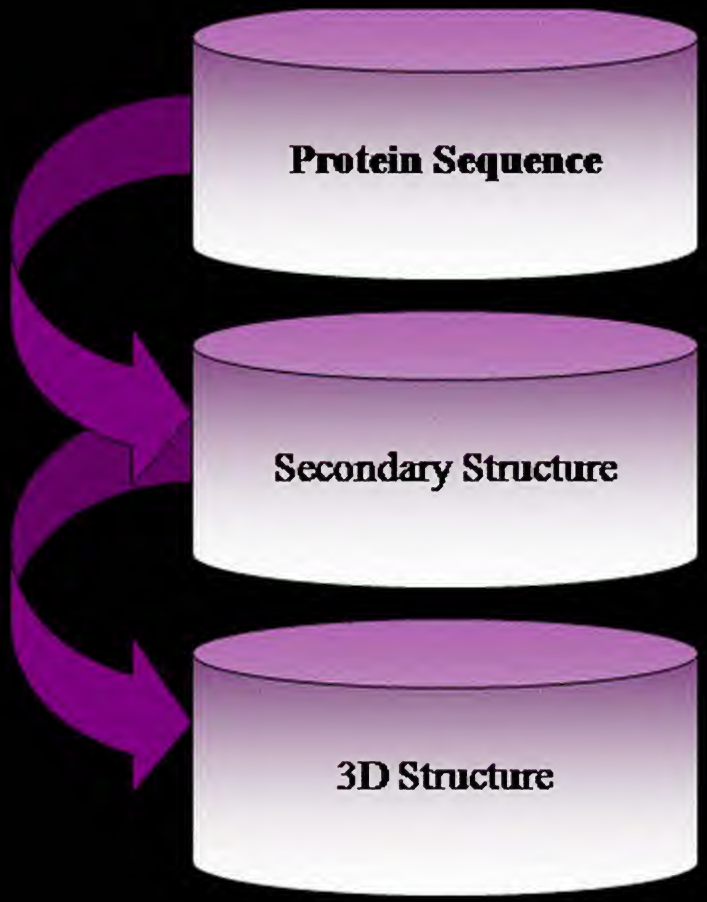
Chemical Nature of Proteins



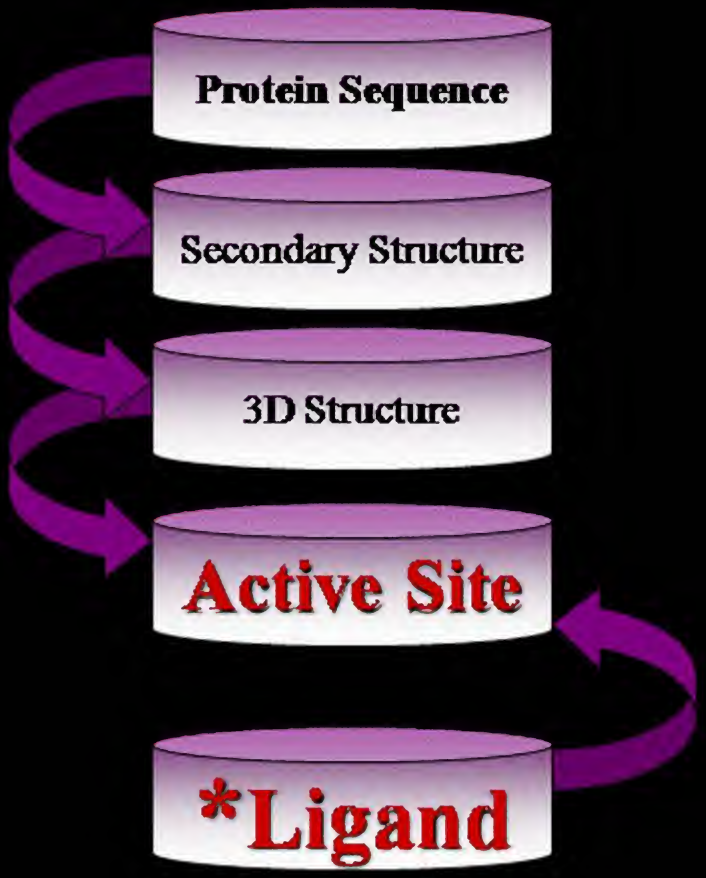
Chemical Nature of Proteins




Chain: A
1
10
20
30
40
50
60
70
80
90
100
110
120
130

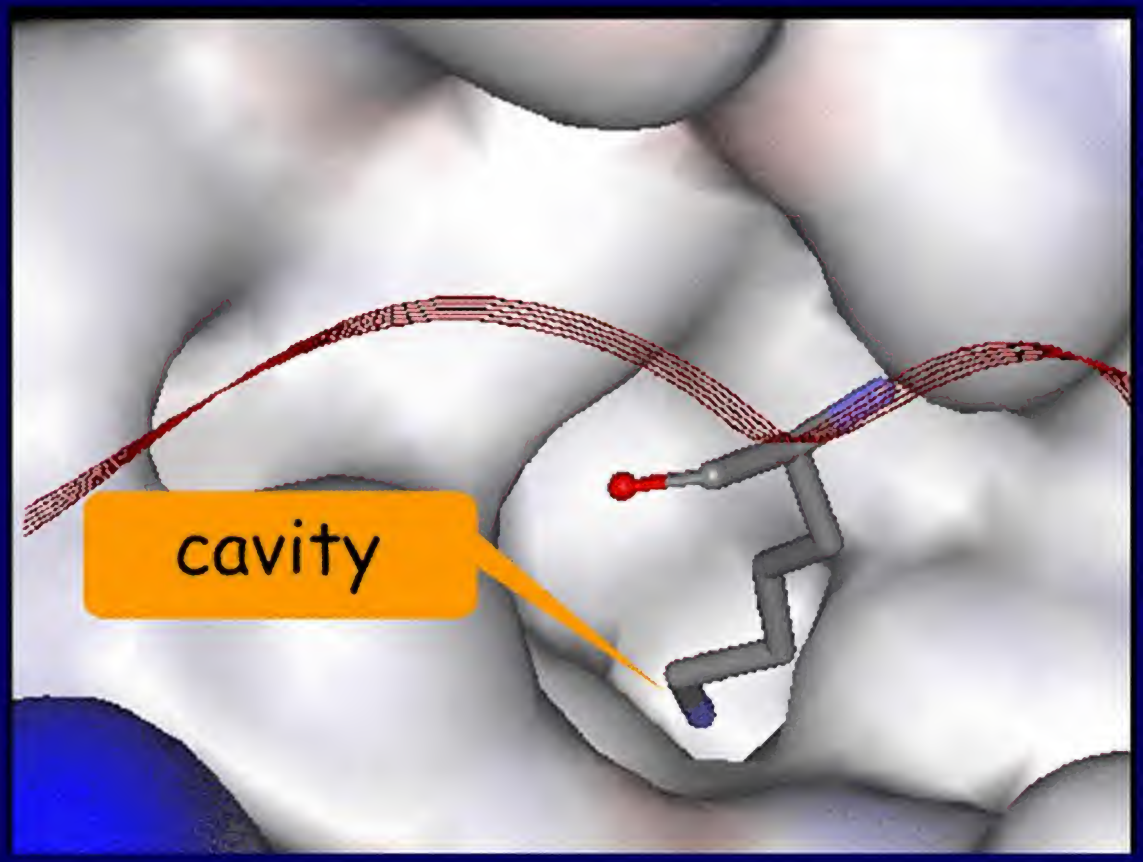

Protein Sequence
Secondary Structure
3D Structure

Molecular Biology Background



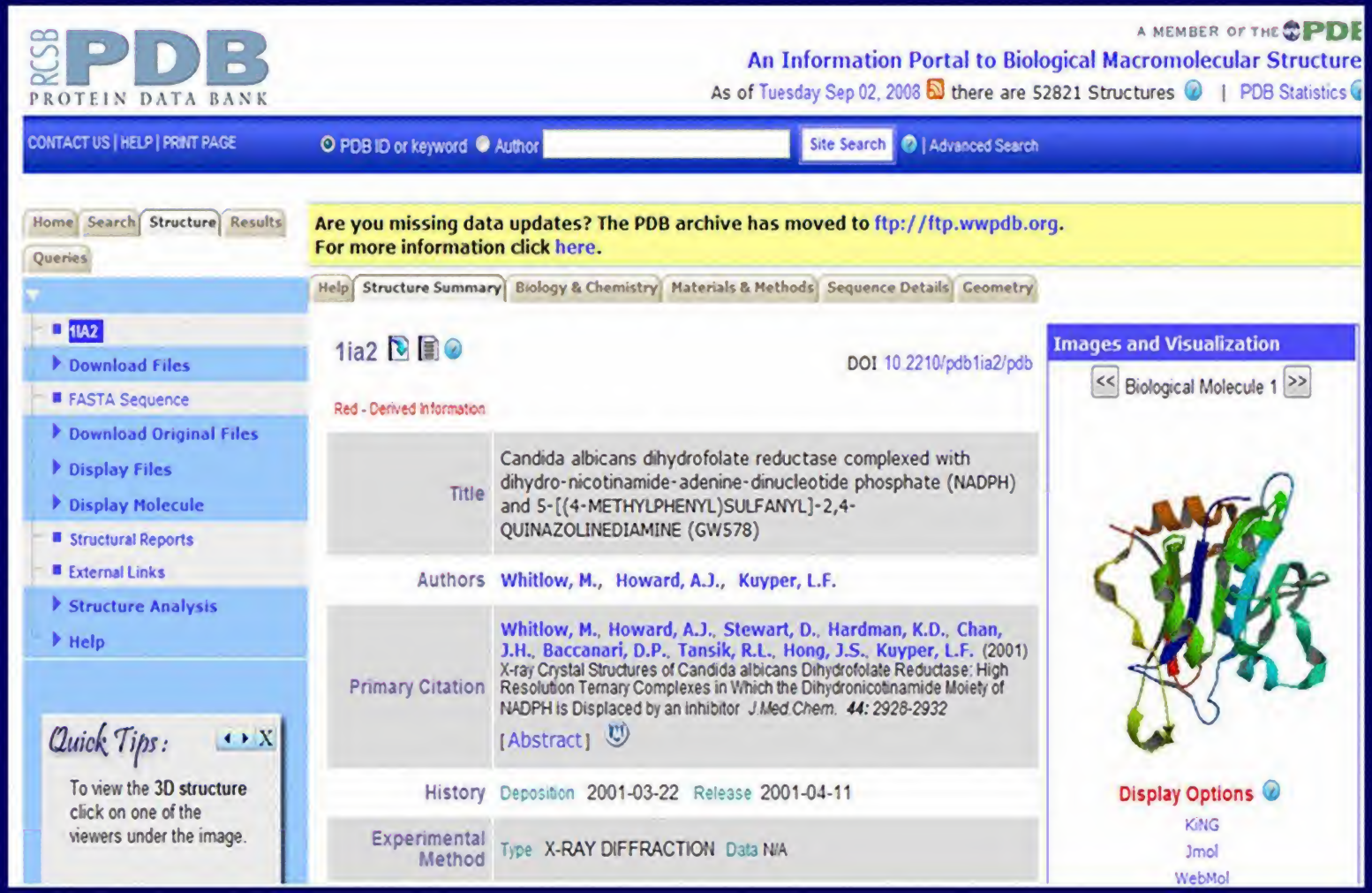
Molecular Biology Background

Active Site

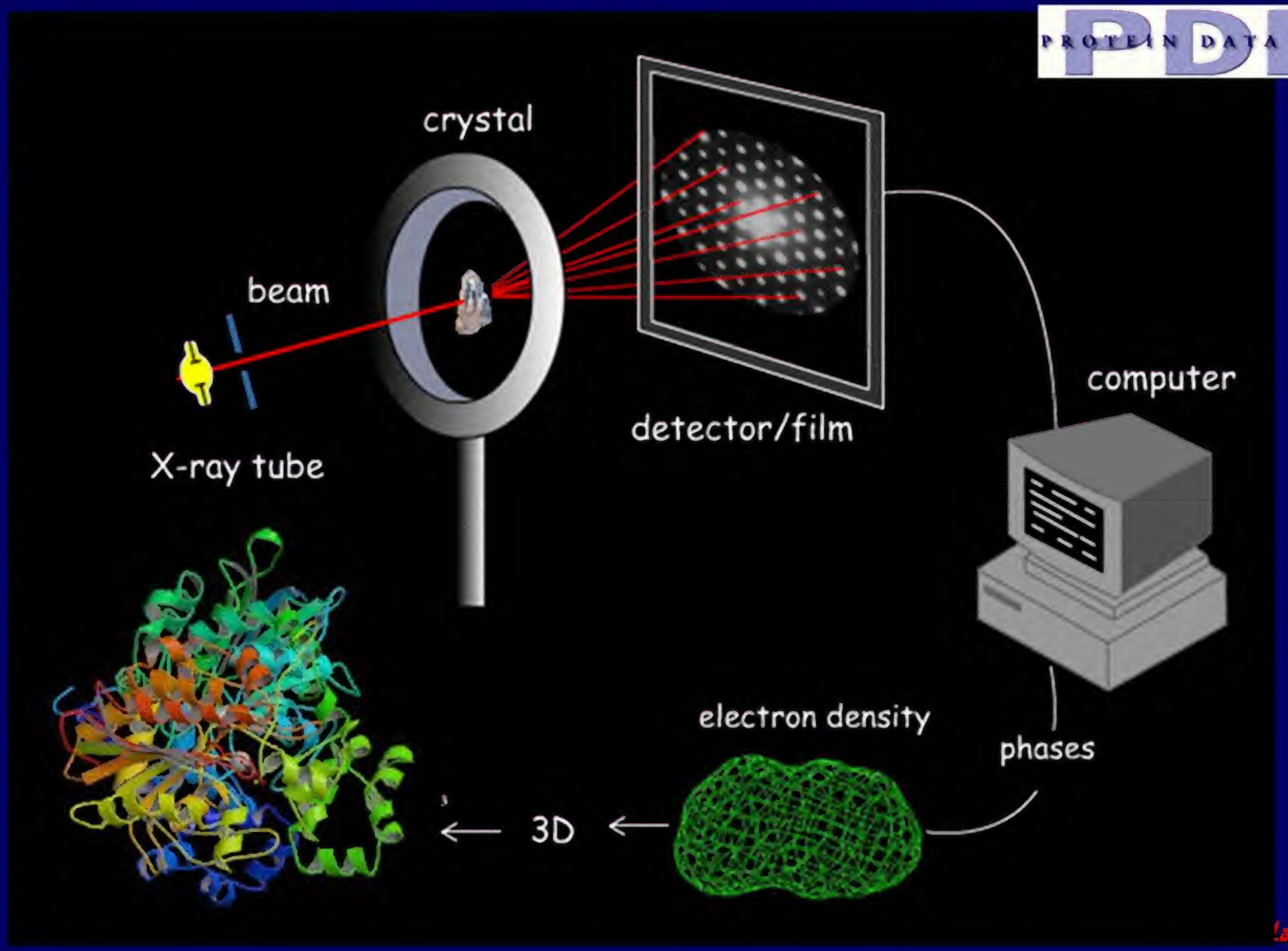


Resources: Protein Data Bank

- Target: Receptors, Enzymes & DNA
- Ligand: agonist & antagonist

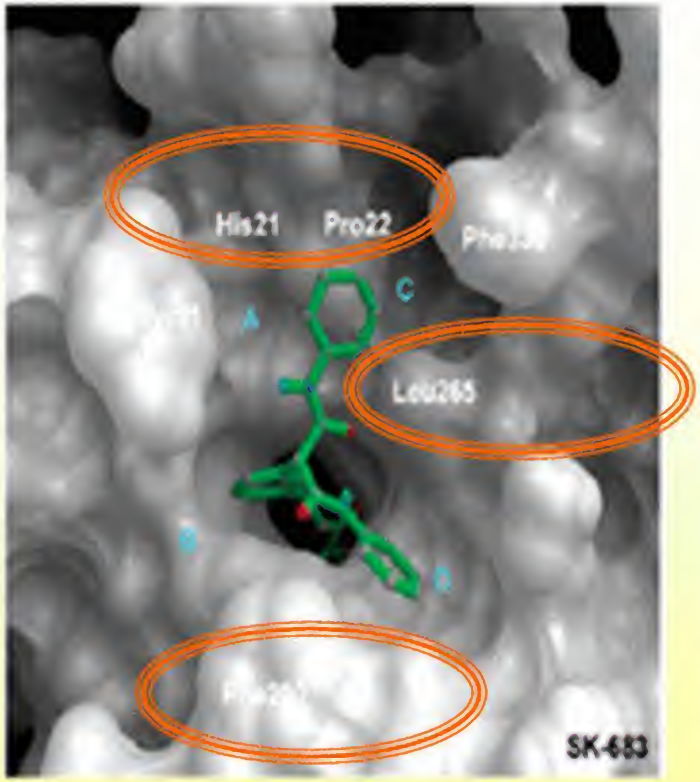


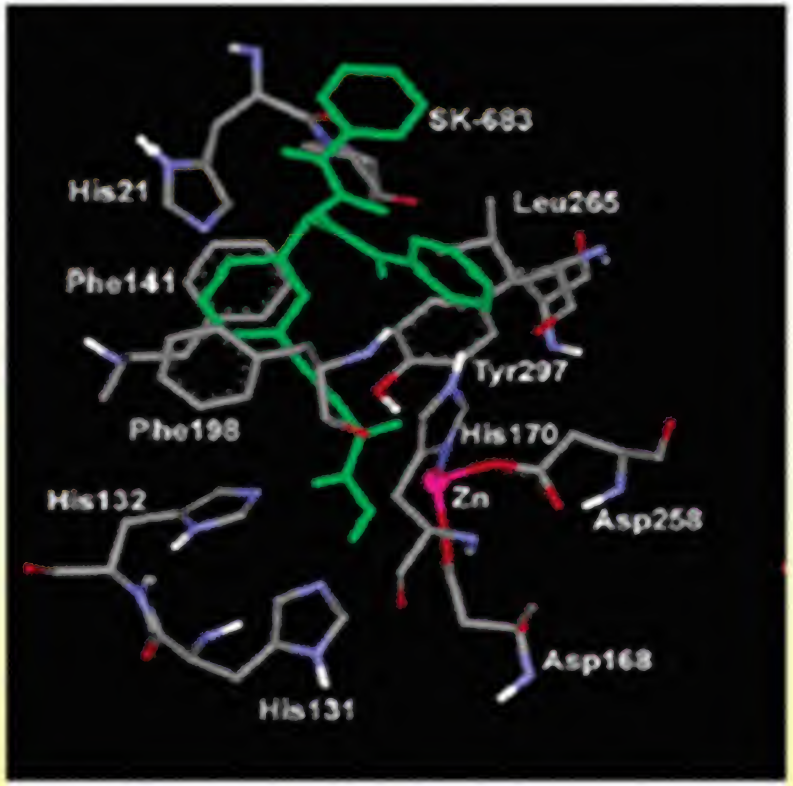
Recourses of Target protein & its Active Site details



Active Site

Catalytic amino acid residues
Key amino acid residues



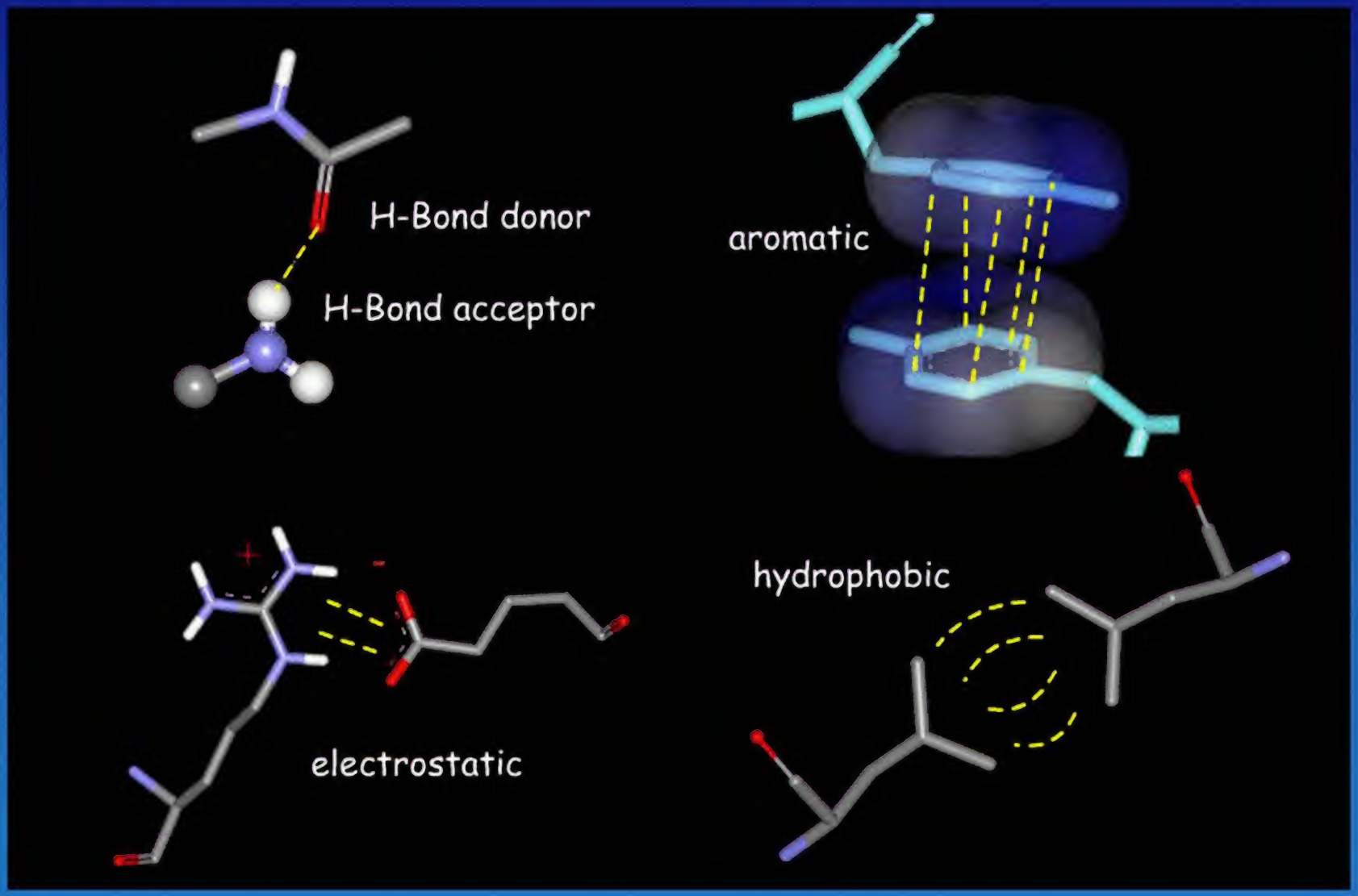


PDB™ PROTEIN DATA BANK

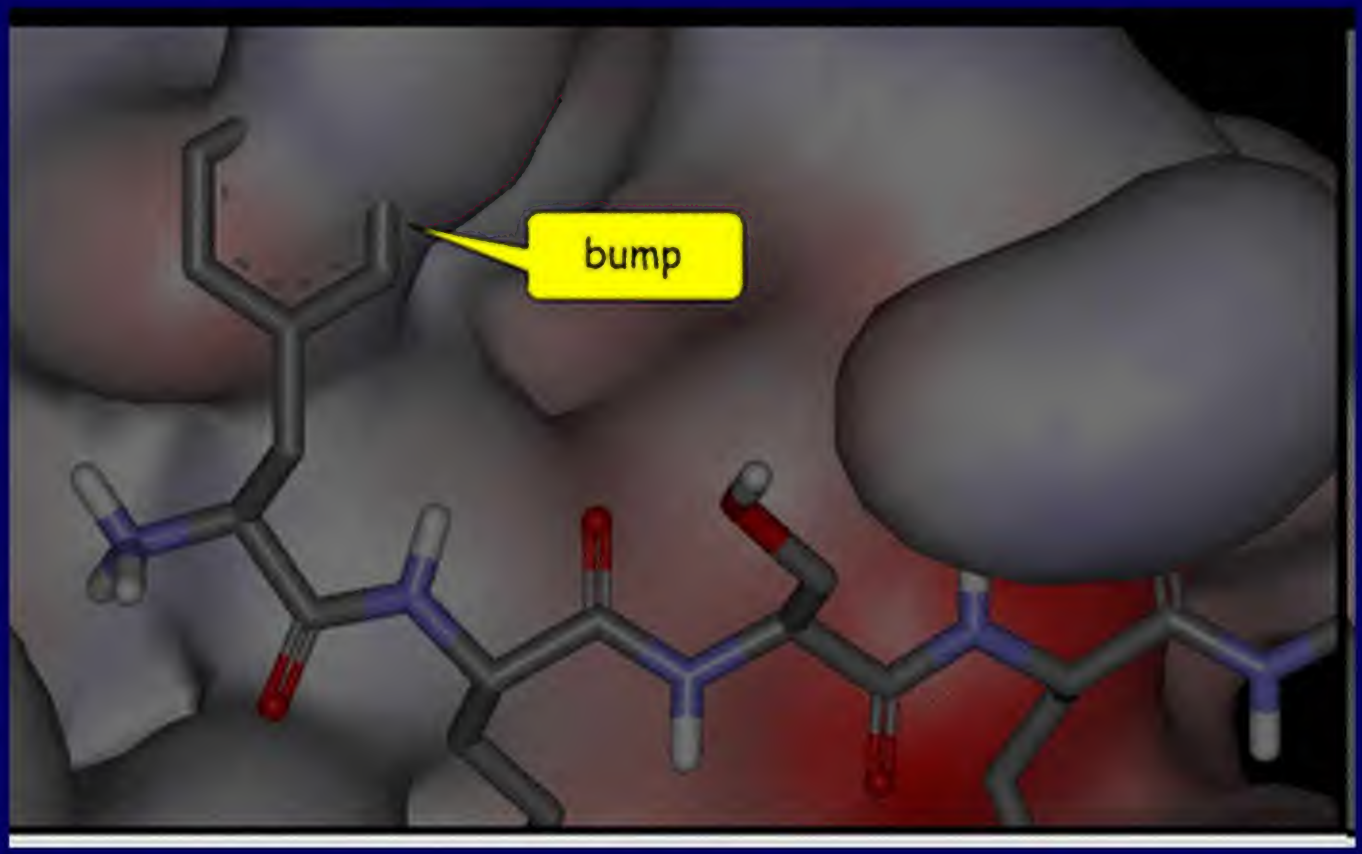
Contacts of ligand

- 3D ligand structure presentation with CHEMSCAPE software (top left window)
- Solvent accessible surface of the ligand complexed with protein and in uncomplexed form (top right window). Clicking on buttons highlights atoms in 3D picture
- List of residues in contact with the ligand
- List of putative hydrogen bonds formed by the ligand
- Full list of atomic contacts formed by the ligand
- Values of ligand complementarity (a function of atomic contact surface area and the chemical properties of contacting atoms)
- Prediction of complementarity changes as a function of atomic substitution in the ligand

Forces Involved in Molecular Recognition

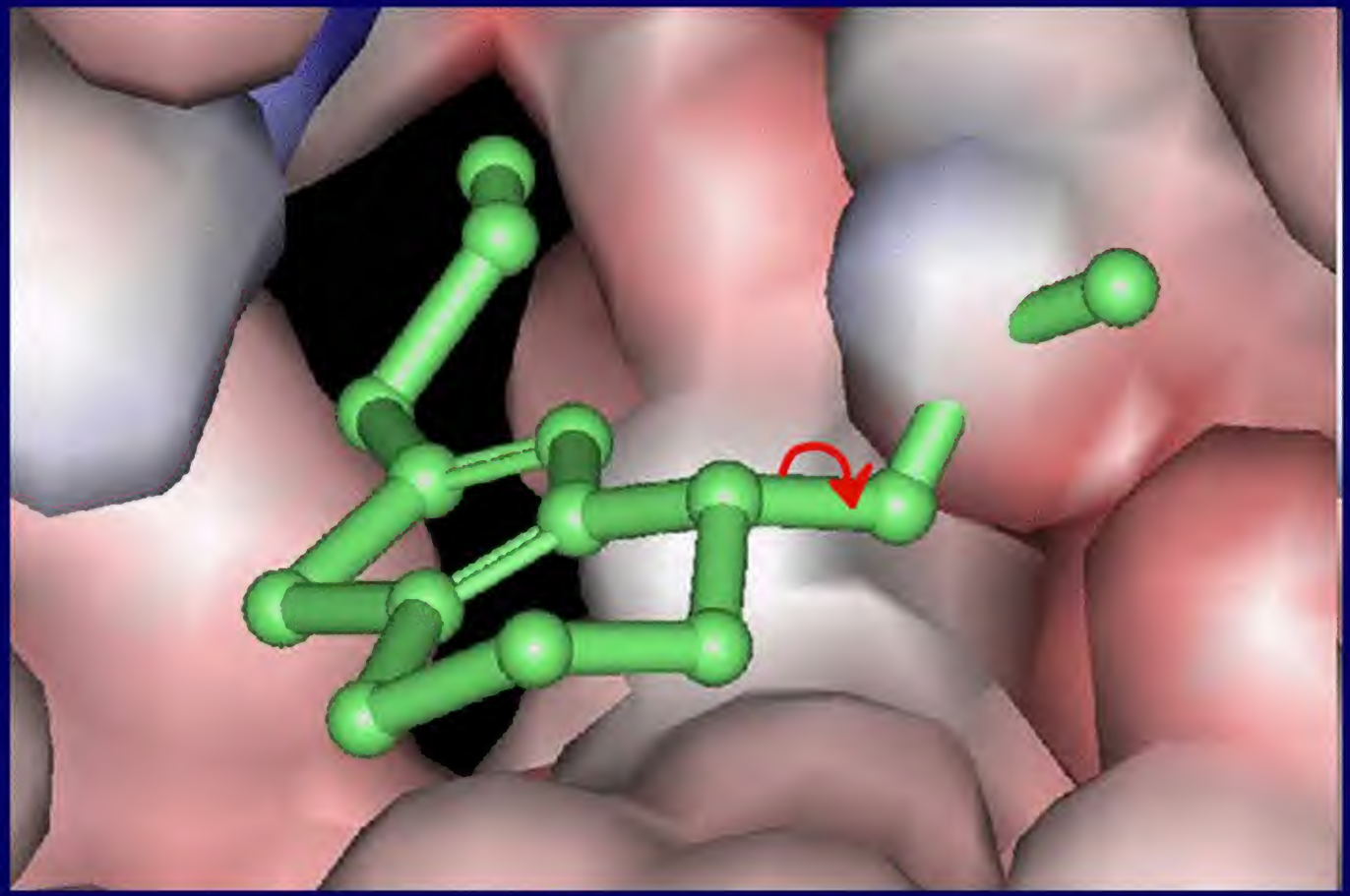


Docking Limitations



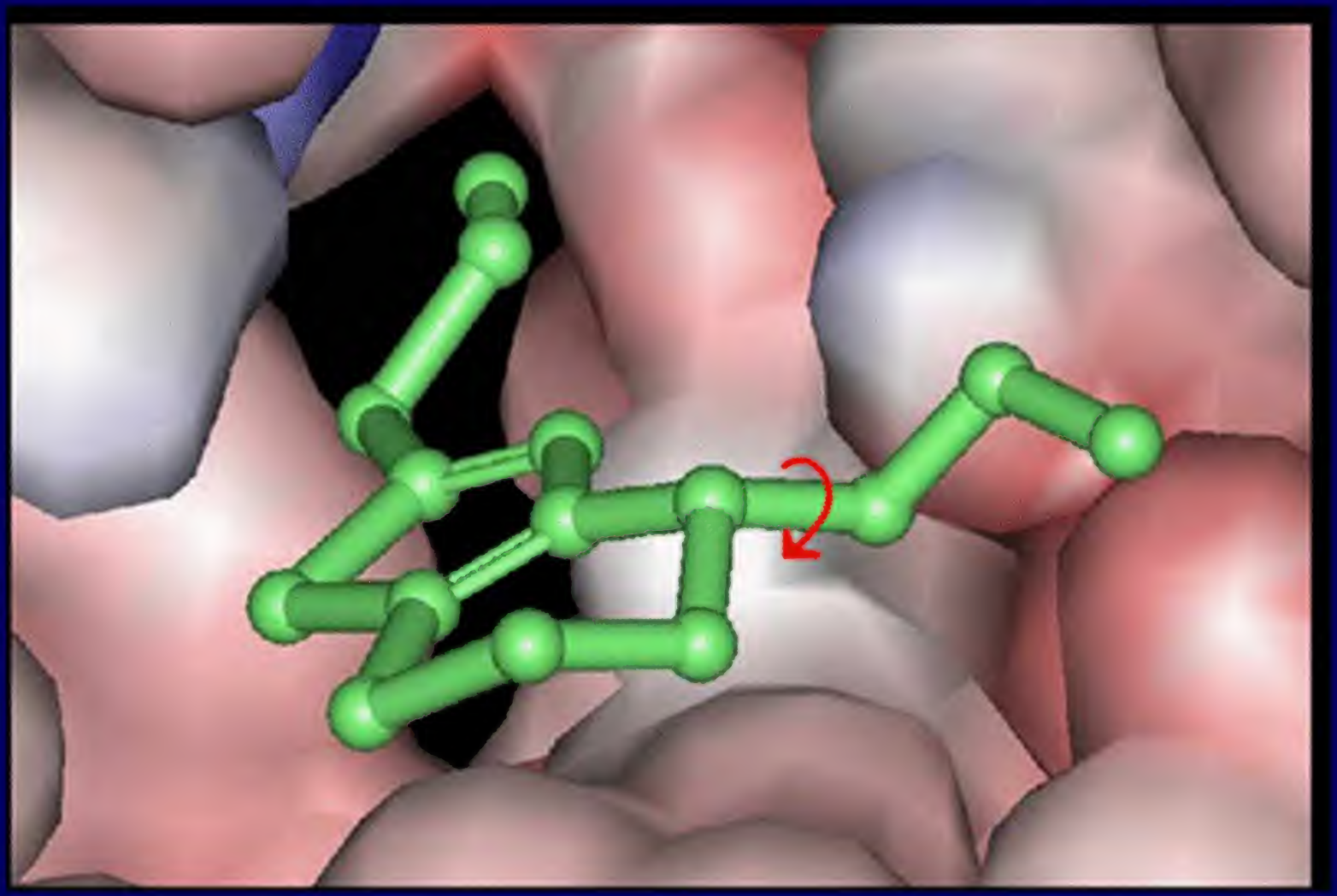
Steric Clashes

Docking Limitations

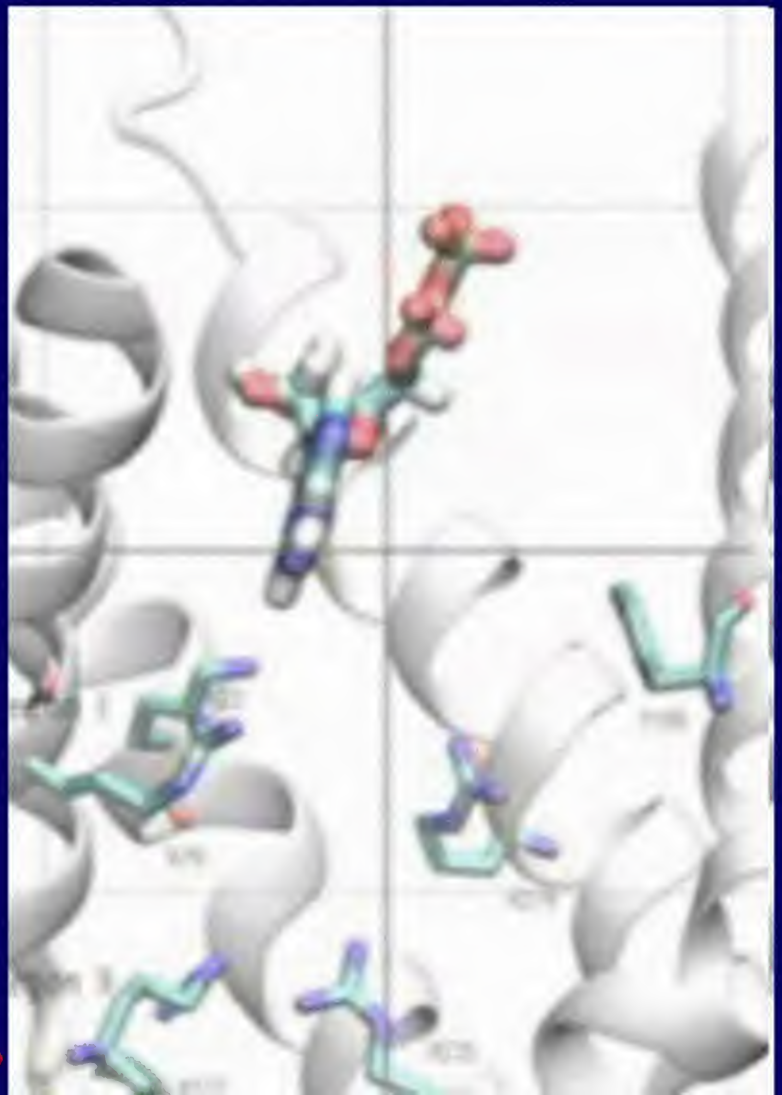


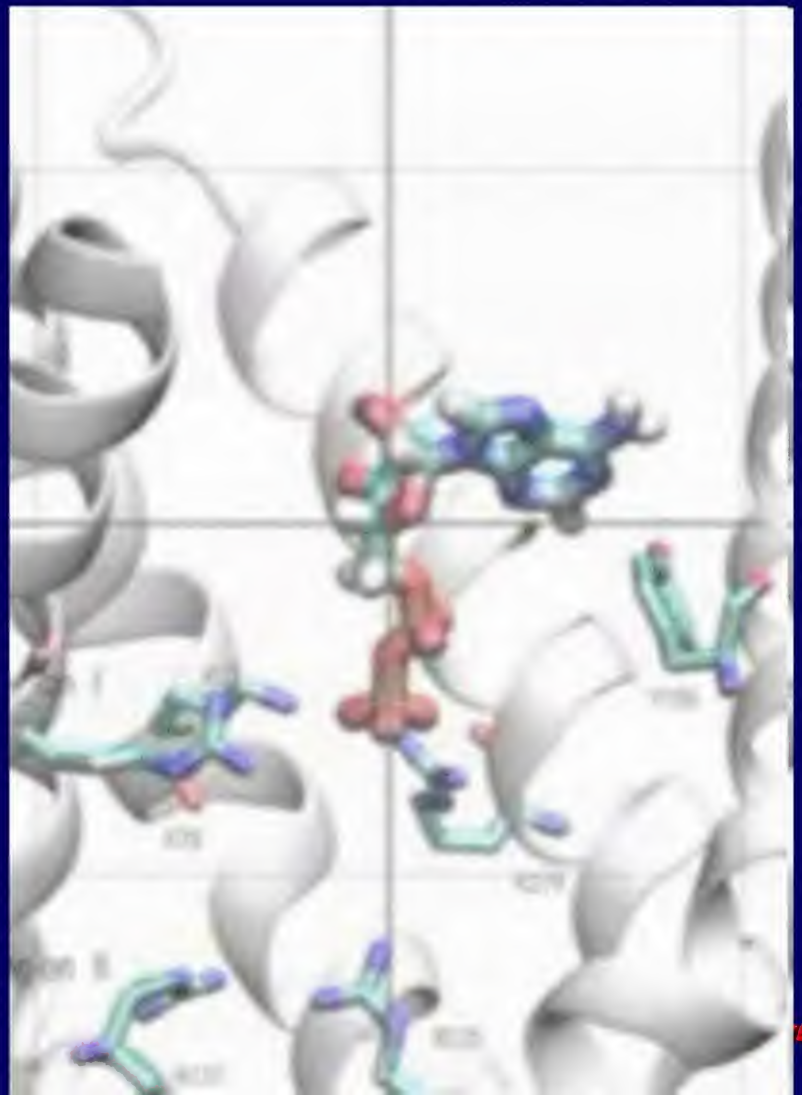
Laila Abou-zeid

Docking Limitations

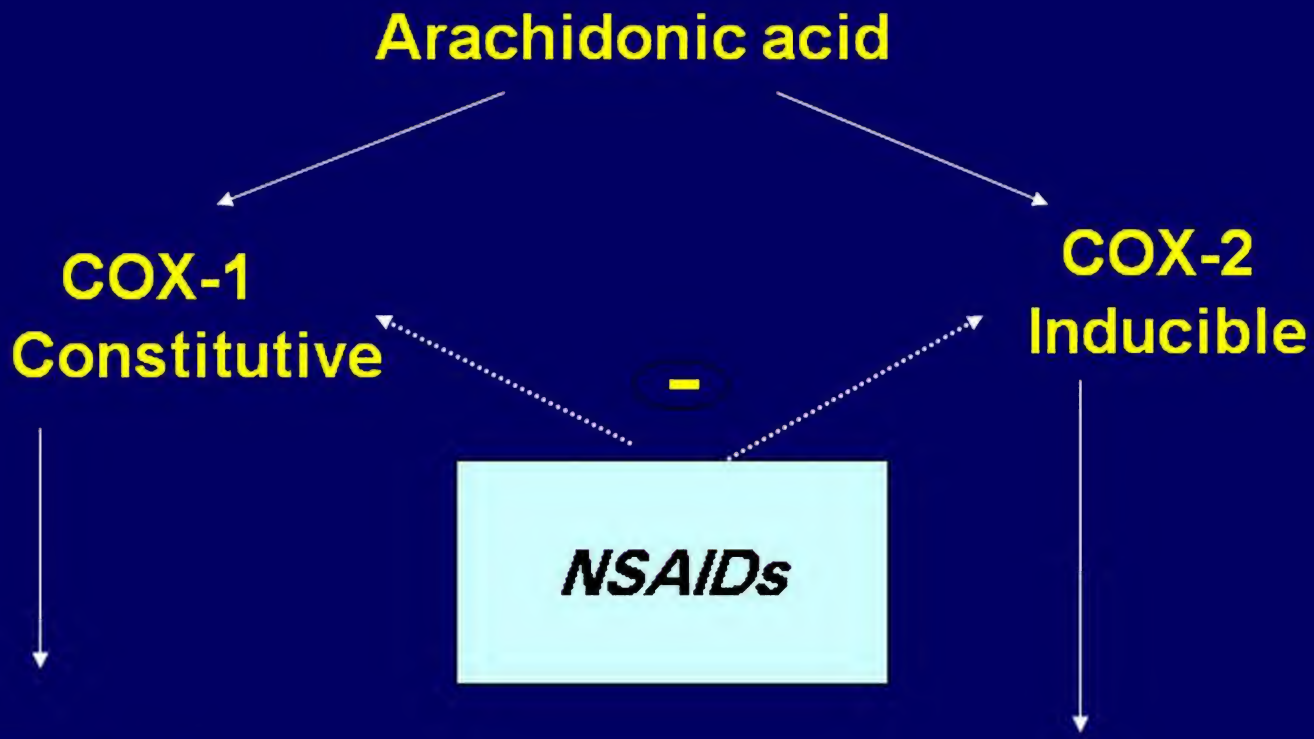


Docking Simulation





Example



Good PGs

- Stomach
- Kidney
- Platelets

Bad PGs

- Macrophages
- Endothelial cells

NCBI

Entrez Structure

My NCBI [Sign In] [Register]

All Databases | PubMed | Nucleotide | Protein | Genome | Structure | PMC | Taxonomy | Books

Search Structure for cyclooxygenase Go Clear Save Search

Limits | Preview/Index | History | Clipboard | Details

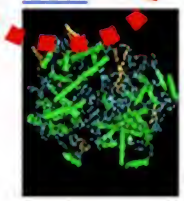
Display Summary Show 20 Sort by Send to Download Cn3D

All: 25 | Bacterial: 0 | Eukaryotic: 25 | Ligand: 25 | NMR: 0 | X-ray: 25

Items 1 - 20 of 25

Page 1 of 2 Next

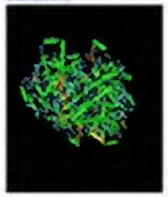
1: 6COX



Related Structures, Literature, Domains, Ligands, Other Links

Cyclooxygenase-2 (Prostaglandin Synthase-2) Complexed With A Selective Inhibitor, Sc-558 In I222 Space Group [mmdbId:54792]

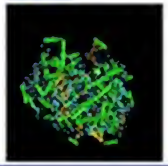
2: 5COX



Related Structures, Literature, Domains, Ligands, Other Links

Uninhibited Mouse Cyclooxygenase-2 (Prostaglandin Synthase- 2) [mmdbId:54761]

3: 4COX



Related Structures, Literature, Domains, Ligands, Other Links

Cyclooxygenase-2 (Prostaglandin Synthase-2) Complexed With A Non-Selective Inhibitor, Indomethacin [mmdbId:54711]

About Entrez

Entrez Structure
Help | FAQ

Structure Research
The NCBI Structure group

MMDB
About Entrez's structure database

CDD
Conserved Domain Database

PDBeast
Taxonomy in MMDB

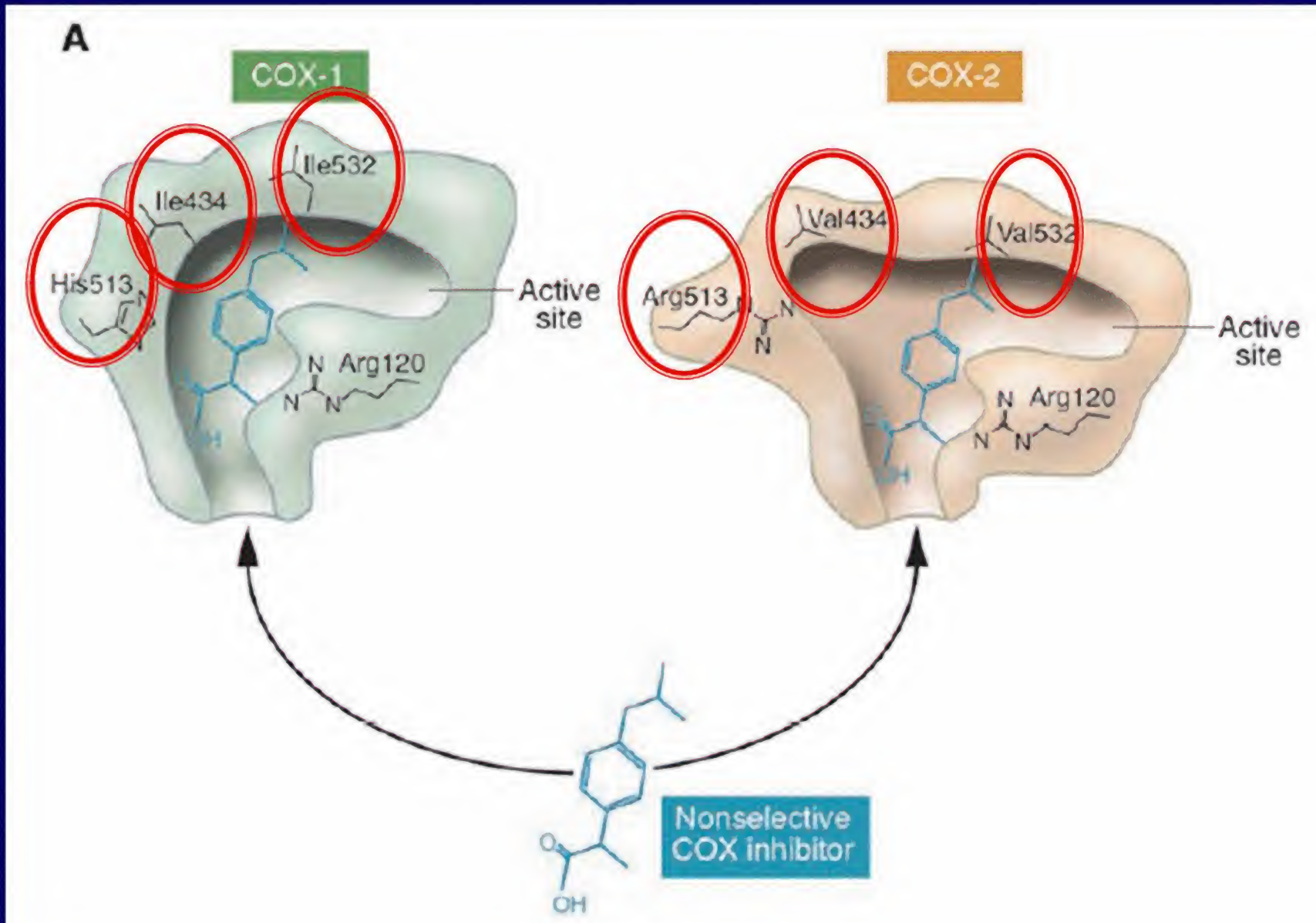
Cn3D NEW
3D-structure viewer

VAST
Structure comparisons

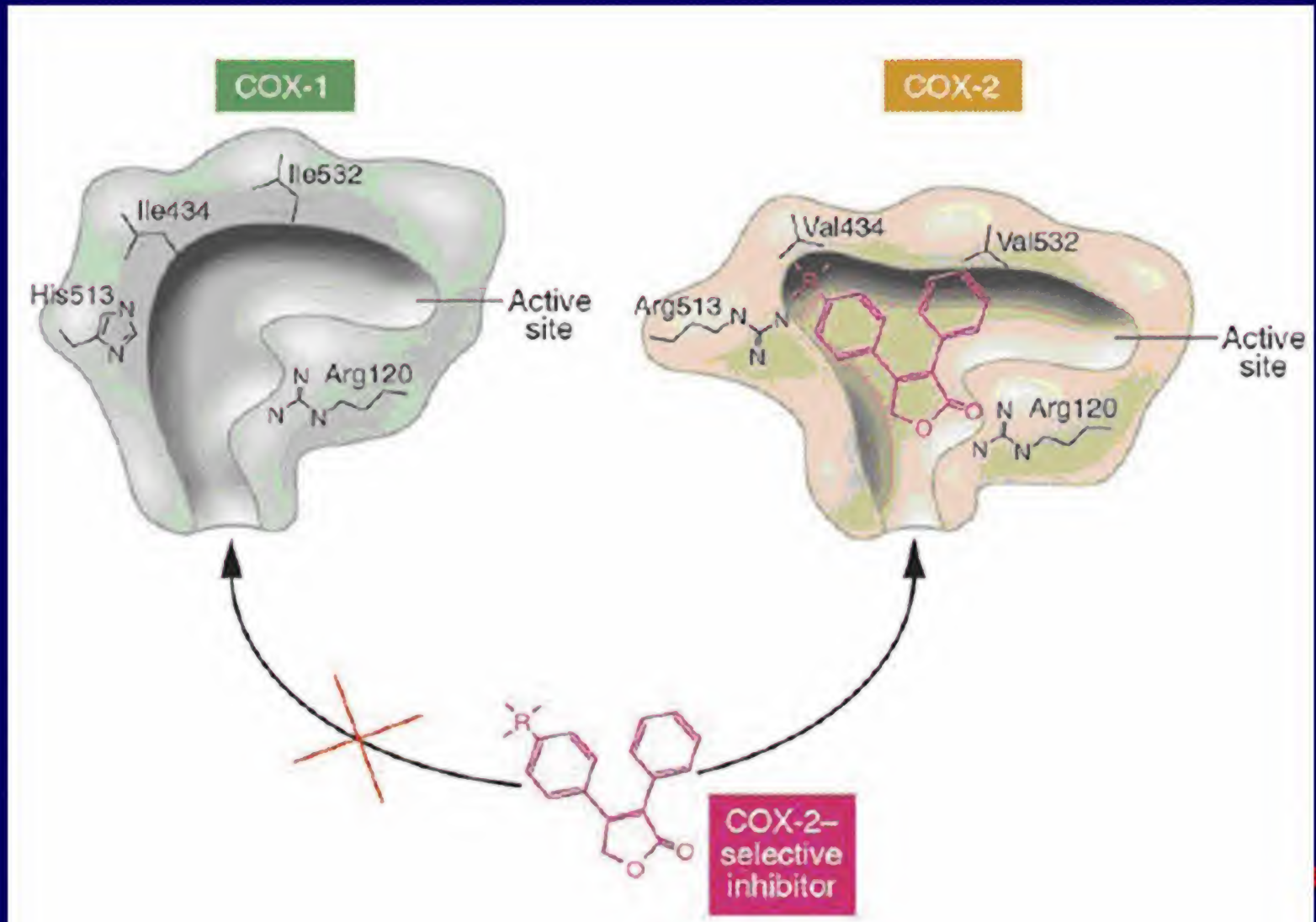
VAST Search
Submit structure database searches

Research

COX1-COX2

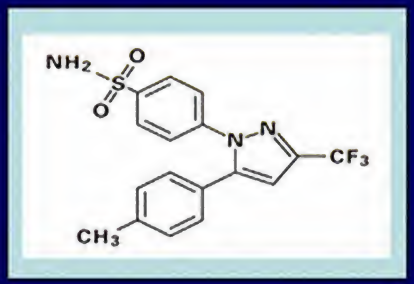

A
COX-1
COX-2
Ile532
Ile434
His513
Active site
N Arg120
Val434
Val532
Arg513
Active site
N Arg120
OH
O
OH
Nonselective COX inhibitor

COX1-COX2


COX-1
COX-2
Ile532
Ile434
His513
Active site
Arg120
Val434
Val532
Arg513
Active site
Arg120
COX-2–selective inhibitor

Celecoxib

50-56



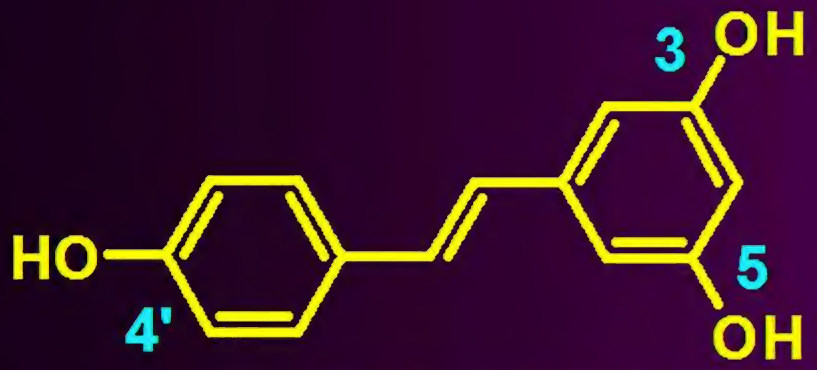
70-72

Compound	R or R_1	R_2	% Inhibition	
			COX-1	COX-2
Control	-	-	-	80.60
55	4-OPh	-	0	59.60
72	4-SCH_3	4-Cl-Bnz	0	60.18

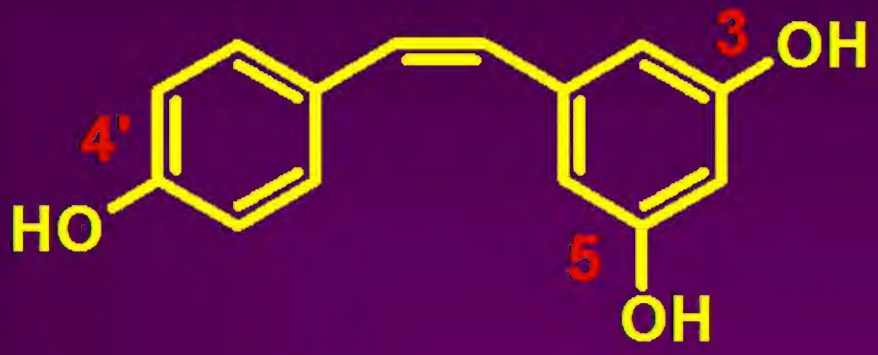
Example

What is in red grapes?

- Resveratrol (RSVL), a phytoalexin that is found in grapes and berries.
- Chemistry: polyphenolic compound



E-Resveratrol



Z-Resveratrol

trans-3,5,4'-trihydroxystilbene (*E*)

cis-3,5,4'-trihydroxystilbene (*Z*)

Resveratrol: Antineoplastic action

Inhibition of Tumor Invasion

- Tumor cells produce proteolytic enzymes named "matrix metalloproteinases" (MMPs).
- MMP enzyme degrades connective tissues & facilitates the invasion of tumor cells to normal tissue.
- RSVL inhibits the activity of matrix metalloproteinase enzyme.

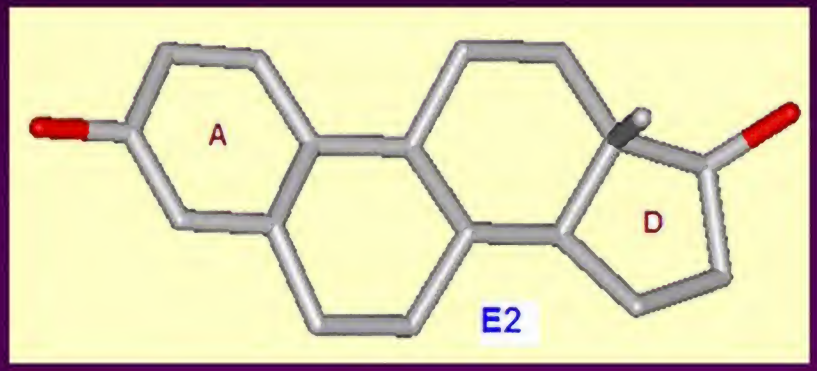
Resveratrol: Antioxidants

Protection Against Atherosclerosis:

- By oxidation LDL becomes electrically unstable & a free radical generator "bad" cholesterol.
- Oxidized LDL circulates in the blood stream penetrates & occupies space within the arterial wall & initiate a cascade of events that lead to coronary artery disease (atherosclerosis).
- Resveratrol effectively scavenges free radicals and inhibits LDL oxidation.

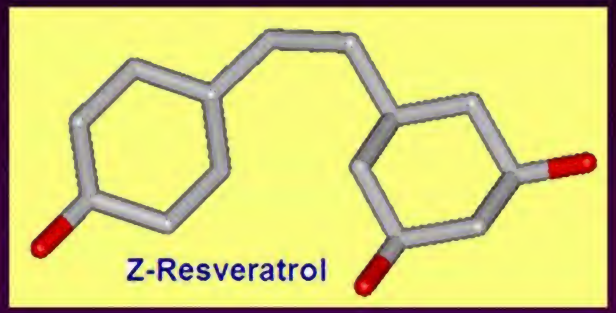
Resveratrol: Mixed Agonist/ Antagonist

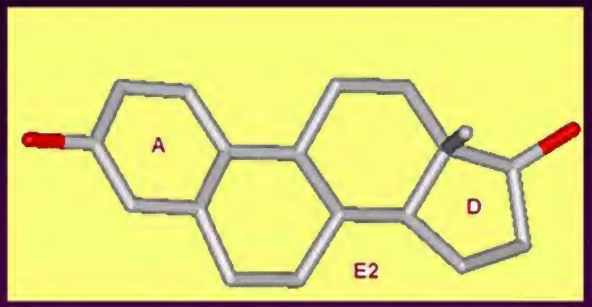
- In estrogen dependant cells RSVL behaves as a **mixed agonist/ antagonist**



- RSVL is <u>an agoinst</u> in absence of E2.

- RSVL is <u>an antagonist</u> in presence E2.



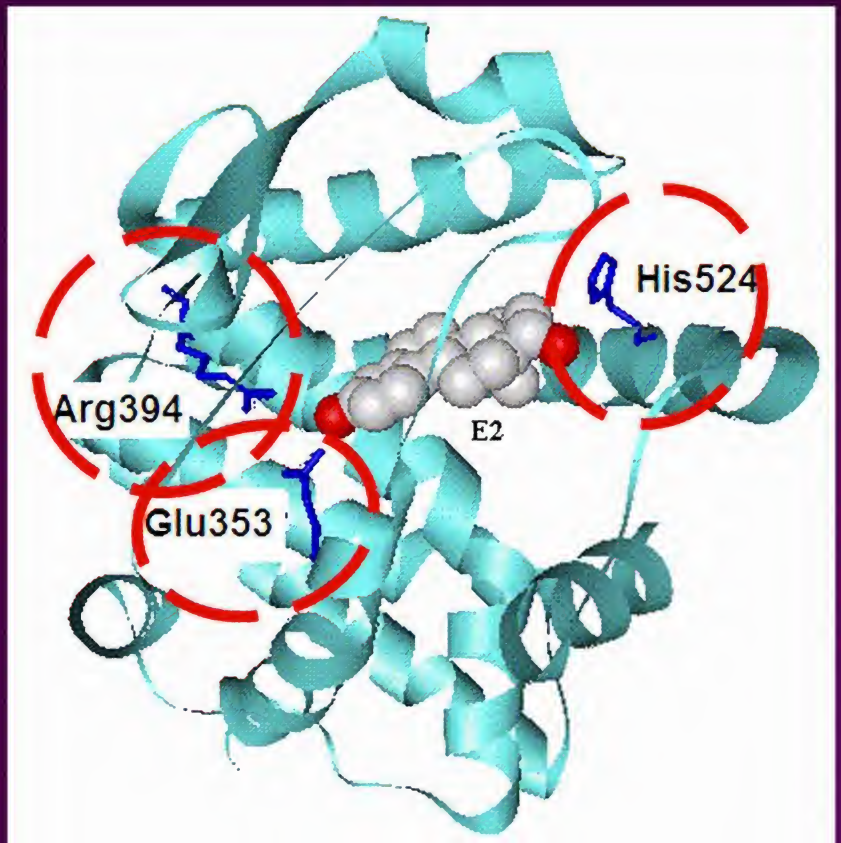


1- **RSVL** has distinct binding characteristics at the **ER-α binding-domain** (pocket) which makes it recognized as a mixed agonist/ antagonist, relative to the pure agonist **Estradiol (E2)**.

2- The *E*-RSVL isomer is more favorably recognized by the human ER-α pocket than the *Z*-isomer.

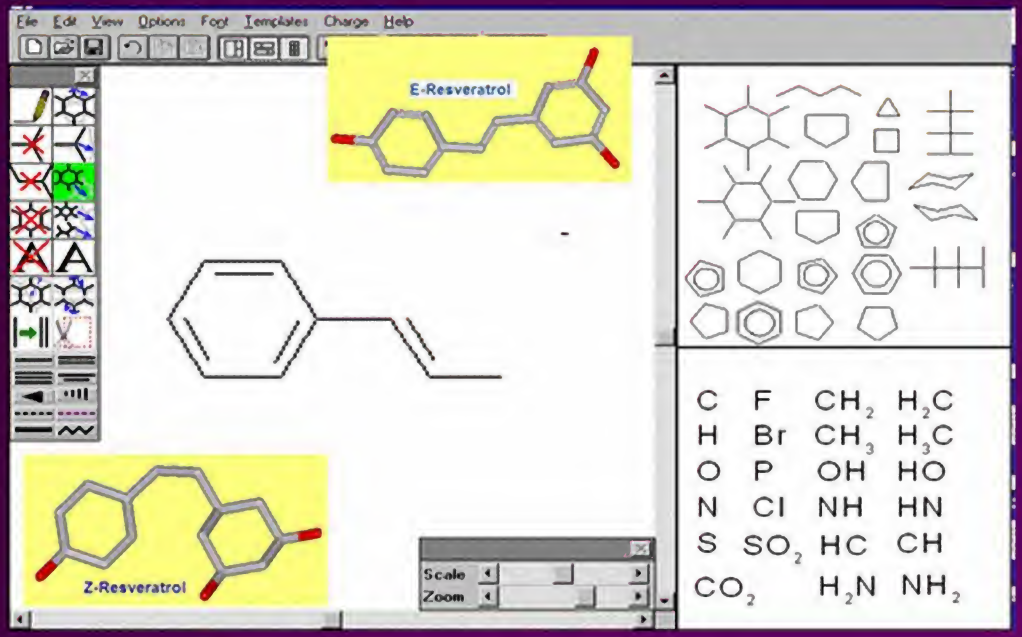
Methodology

- *Download the crystalline structure of the Estrogen receptor from the online Protein data Bank website PDB.*
- *define the key amino acids in the active binding site.*

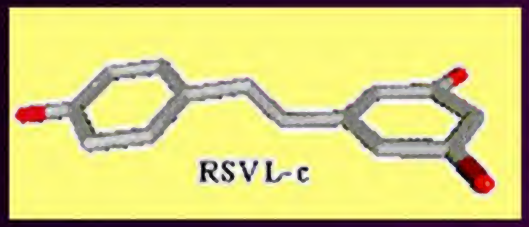


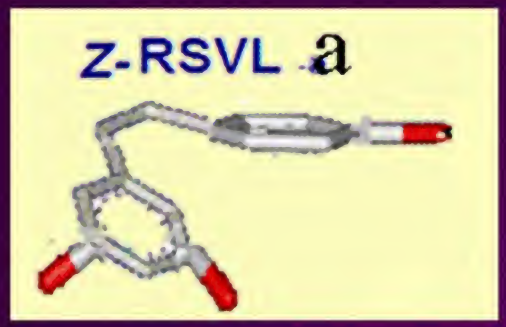
- *Building up the structure of E-RSVL.*

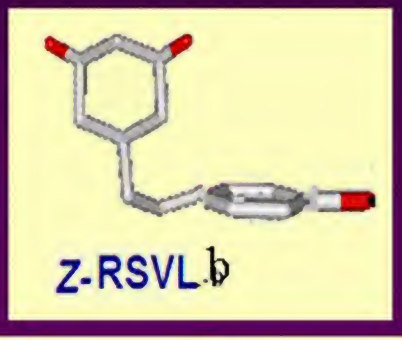
- *(E)- and (Z)*-RSVL were constructed using HyperChem6.
- Partial atomic charges were assigned with the semiemperical mechanical calculation method "AM1" using HyperChem6.

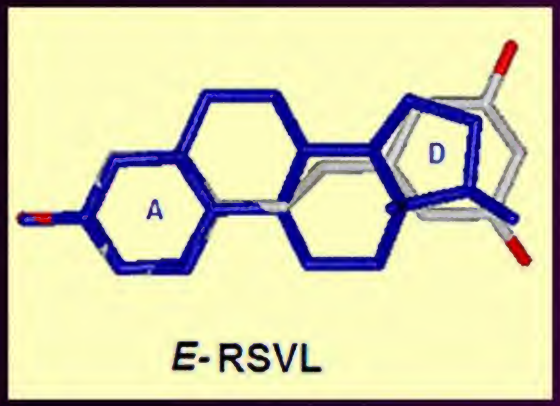


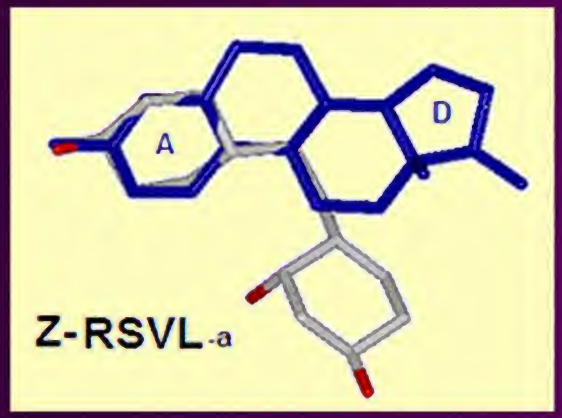
- *Conformational search for the lowest energy conformer for each isomer of Resveratrol*
- Possible orientations of the lowest *conformer for each isomer was* aligned on the E2 crystal structure. RSVL models were generated by alignment of the phenolic A-rings

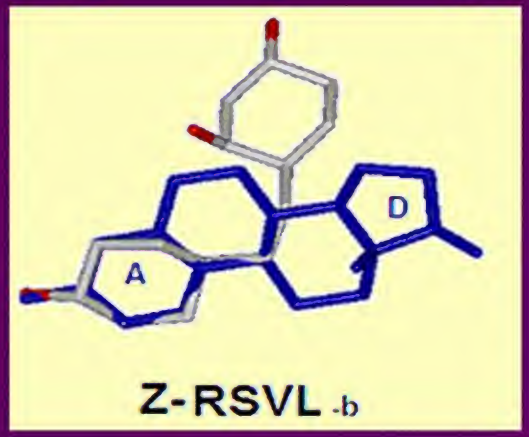








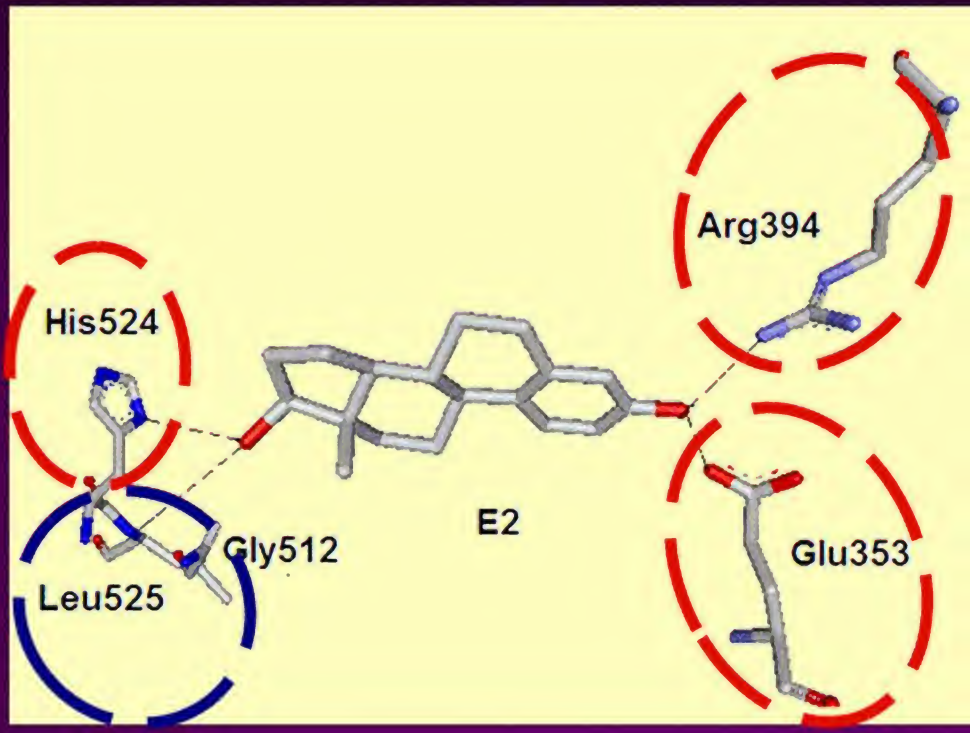




Results

100 PS Dynamic simulation & binding mode of "E2"

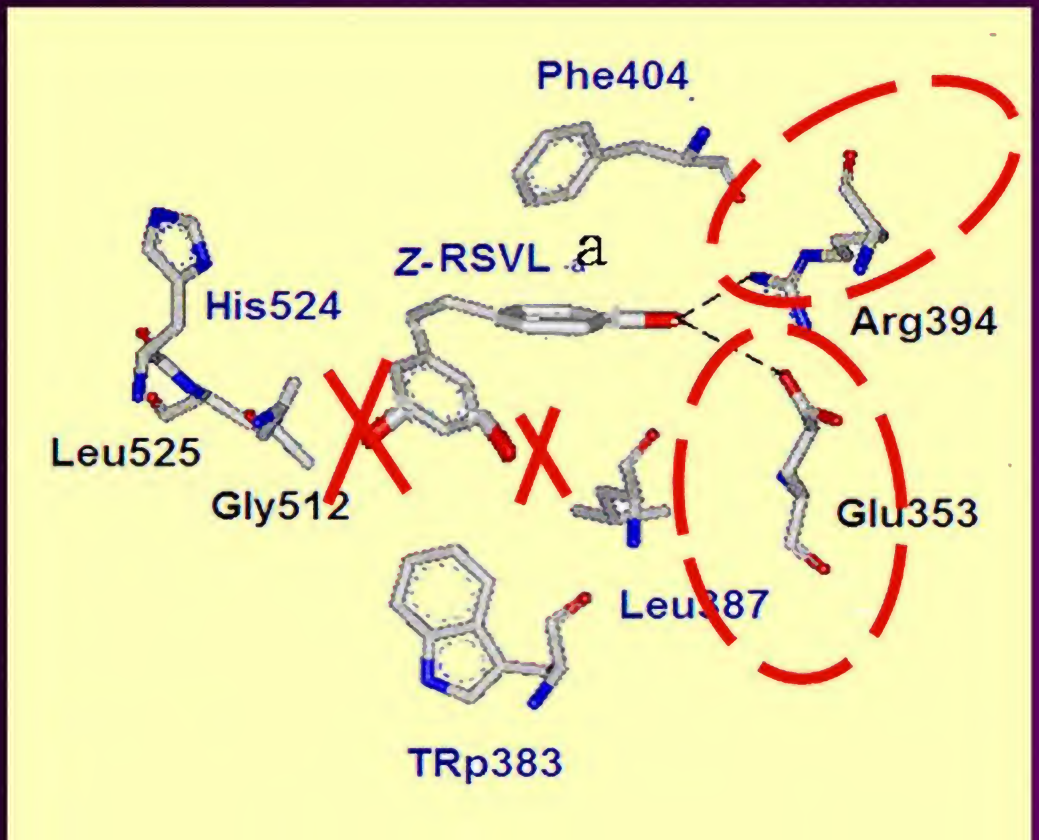
At 0ps: The docked E2 was initially recognized by 3HB with the active site residues (catalytic triad: Arg394, Glu353 and His524) which are known to be essential for the reading of agonistic activity.



- At 100ps MD, a fourth HB between the 17-OH group of E2 and Leu525 was also evident.

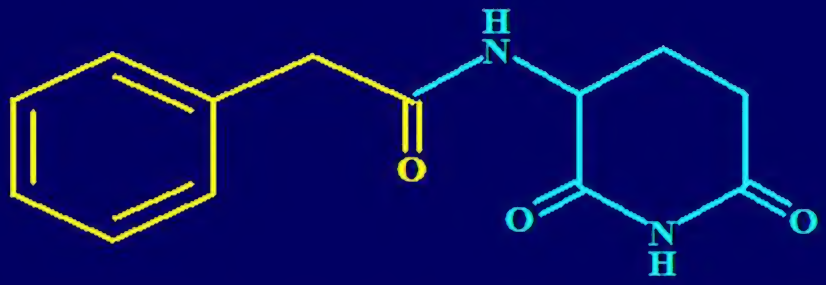
Dynamic simulation studies during 100 PS & binding mode of "(Z)-RSVL-a"

- (Z)-RSVL-a formed bifurcated (2HB) with only two pocket residues (Arg394, and Glu353) through its 4'-hydroxyl group of A-ring, whereas its 3- and 5-OH groups remained unengaged.



Example

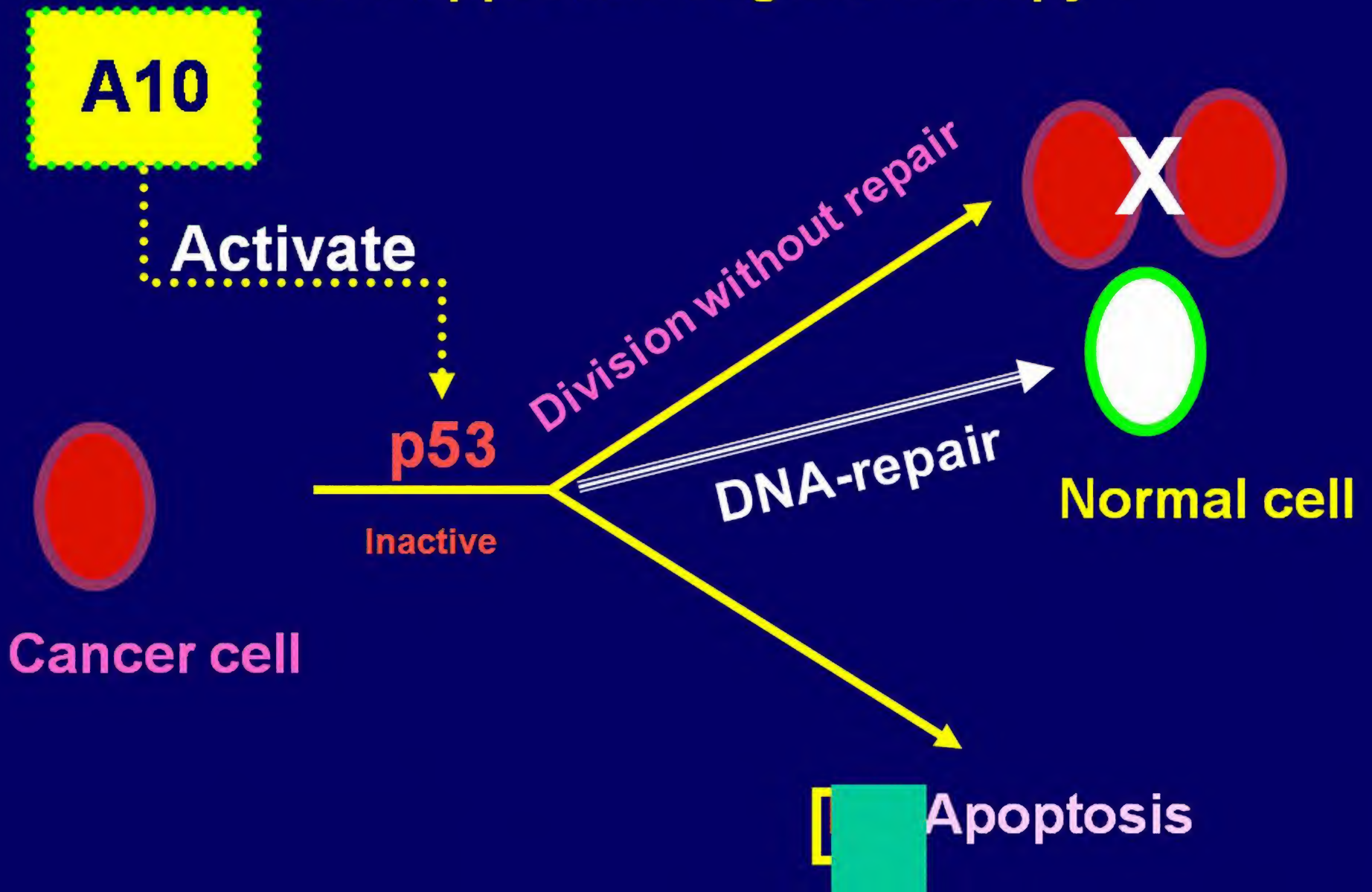
Antineoplaston (A10): an endogenous cancer protective agent (Burzynski, 1973)



3-(Phenylacetylamino) -2,6-piperidinedione “A10”

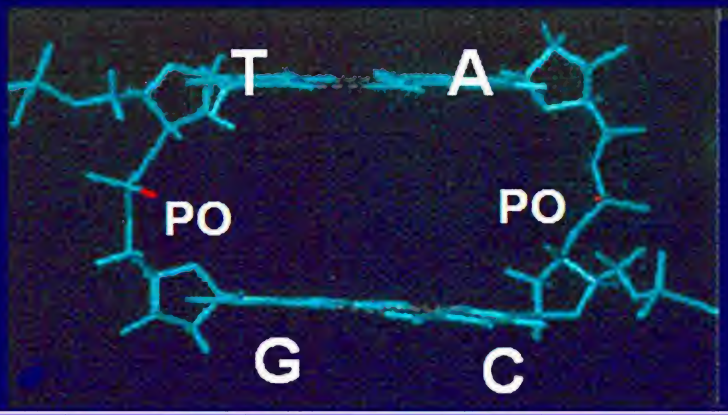
2- Augment tumor cell apoptosis:

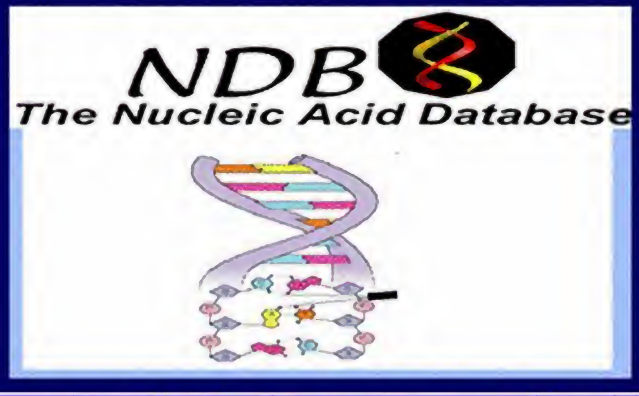
a new approach of gene therapy ?

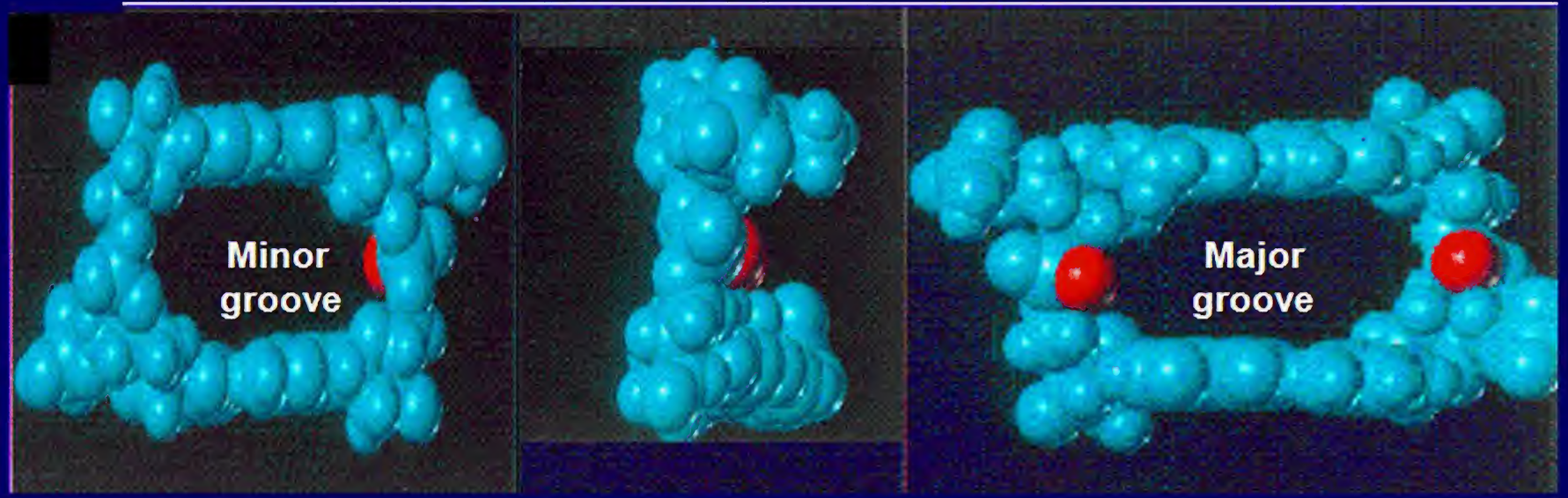


DNA as a receptor for de novo drug design

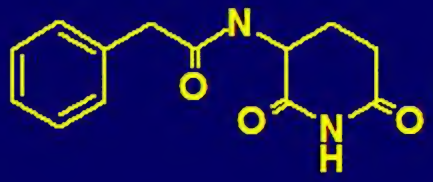
DNA base pair sequence





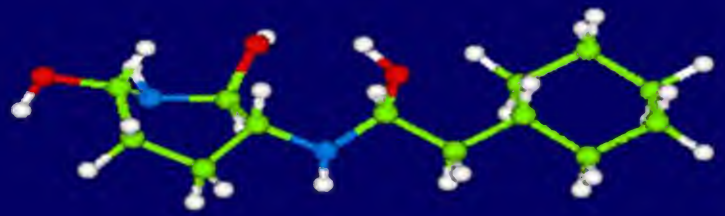


Docking of A10 into DNA

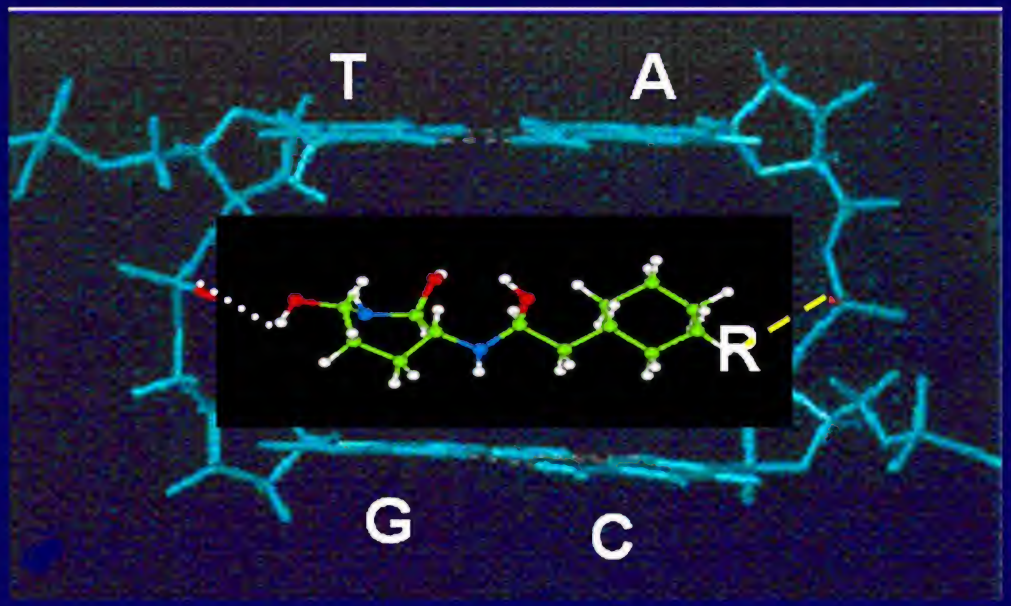


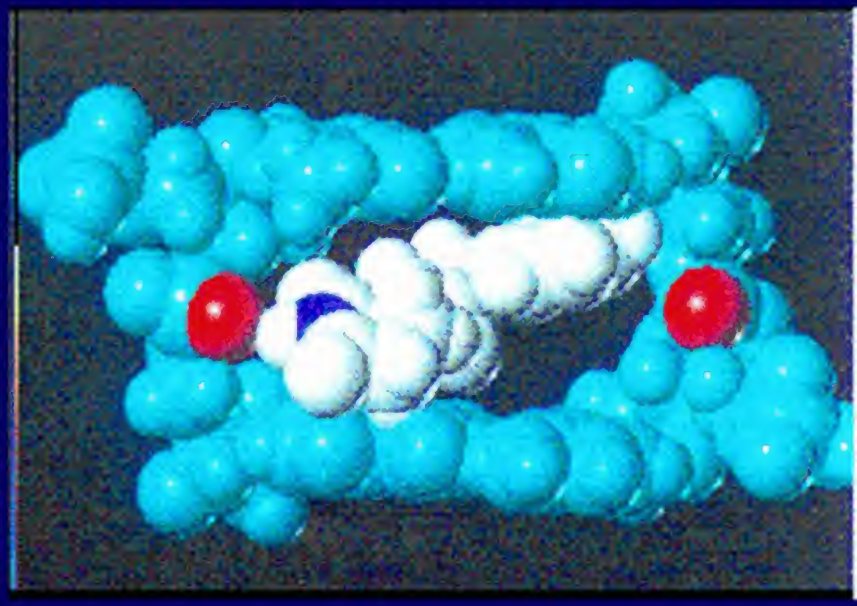
3D-generation

Energy minimization



A10

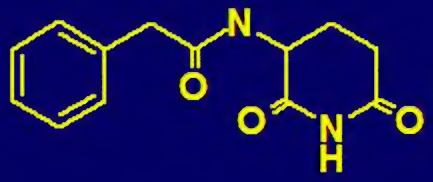




DNA complementarity α Docking energy(-)

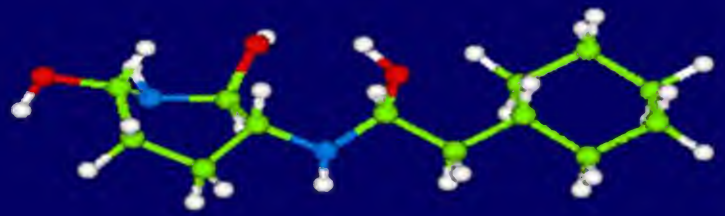
Docking energy = $E_{elect} + E_{vdw} + E_{HB}$

Docking of A10 into DNA

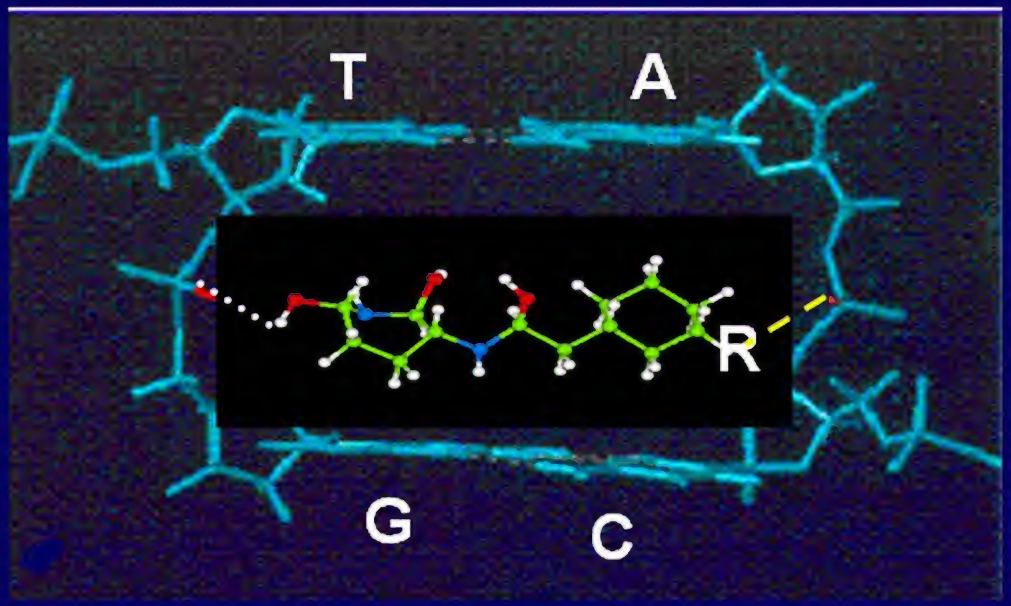


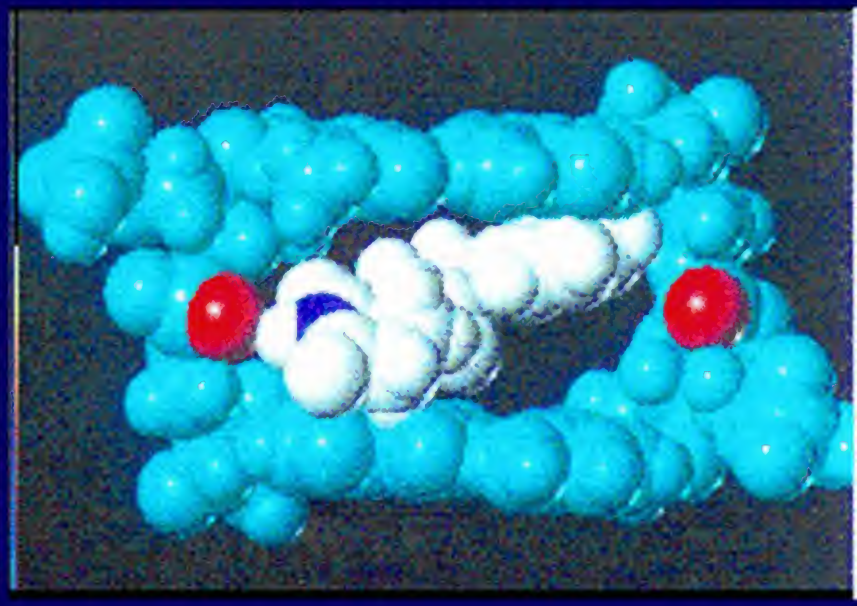
3D-generation

Energy minimization



A10

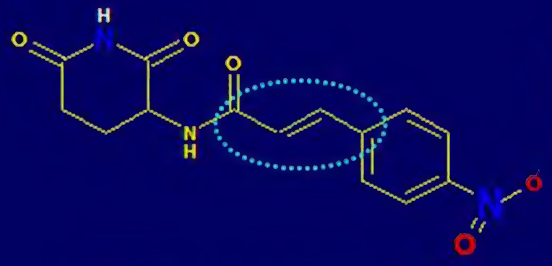




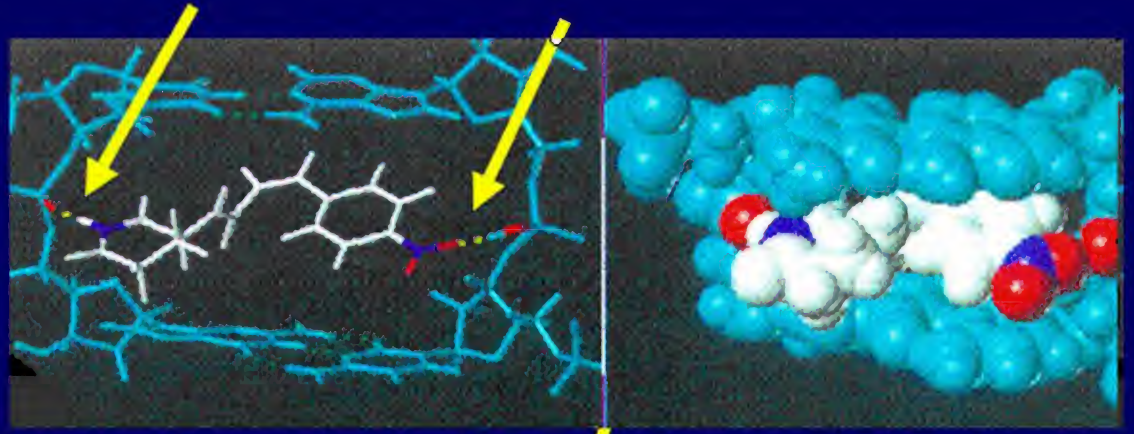
DNA complementarity α Docking energy(-)

Docking energy = $E_{elect} + E_{vdw} + E_{HB}$

Interpretation of docking energy values in light of the structural features of A10 analogs

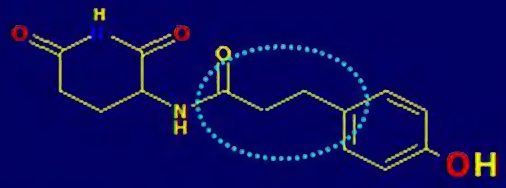


p-NO2-cinnamoyl-A10

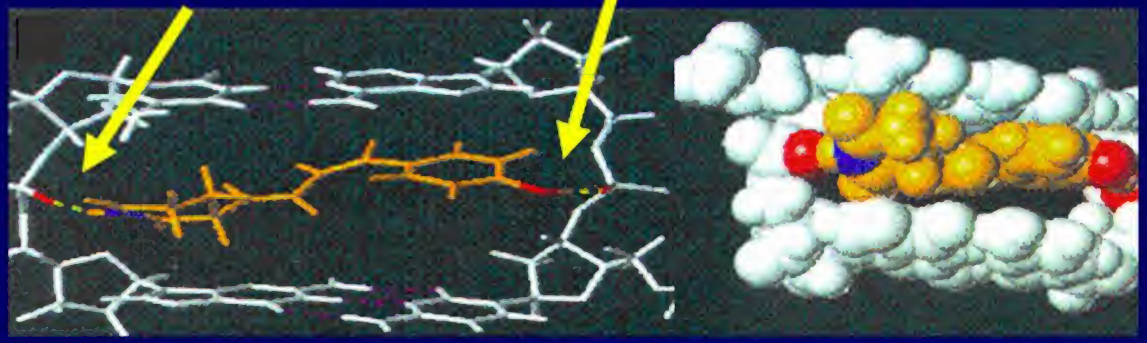


Relative docking energy

160%

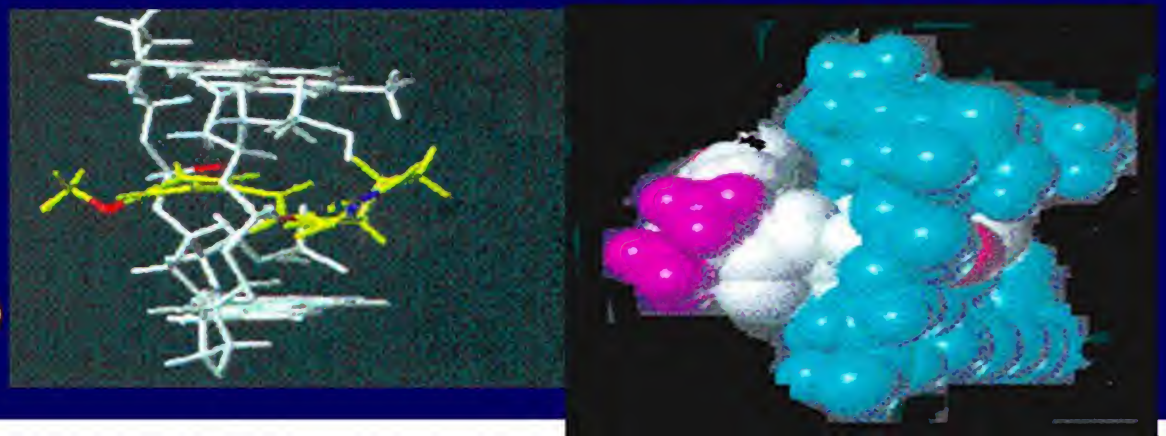


p-HO-propionoyl-A10



157%

p-MeO-propionoyl-A10



65%

THANK YOU